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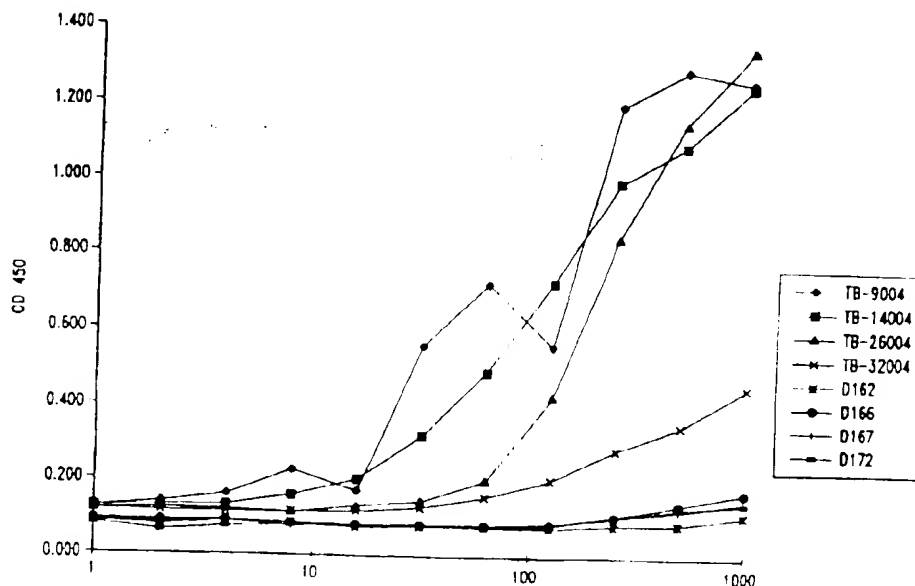
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(54) Title: COMPOUNDS AND METHODS FOR DIAGNOSIS OF TUBERCULOSIS



Diagnostic kits containing such polypeptides or DNA sequences and a suitable detection reagent may be used for the detection of *M. tuberculosis* infection in patients and biological samples. Antibodies directed against such polypeptides are also provided.

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Description

## COMPOUNDS AND METHODS FOR DIAGNOSIS OF TUBERCULOSIS

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Technical Field

The present invention relates generally to the detection of *Mycobacterium tuberculosis* infection. The invention is more particularly related to polypeptides comprising a *Mycobacterium tuberculosis* antigen, or a portion or other variant thereof, and the use of such polypeptides for the serodiagnosis of *Mycobacterium tuberculosis* infection.

Background of the Invention

20 Tuberculosis is a chronic, infectious disease, that is generally caused by infection with *Mycobacterium tuberculosis*. It is a major disease in developing countries, as well as an increasing problem in developed areas of the world, with about 8 million new cases and 3 million deaths each year. Although the infection may be asymptomatic for a considerable period of time, the disease is most commonly  
25 manifested as an acute inflammation of the lungs, resulting in fever and a nonproductive cough. If left untreated, serious complications and death typically result.

Although tuberculosis can generally be controlled using extended antibiotic therapy, such treatment is not sufficient to prevent the spread of the disease.

although compliance with the treatment regimen is critical, patient behavior is difficult to monitor. Some patients do not complete the course of treatment, which can lead to ineffective treatment and the development of drug resistance.

Inhibiting the spread of tuberculosis will require effective vaccination and accurate, early diagnosis of the disease. Currently, vaccination with live bacteria is the most efficient method for inducing protective immunity. The most common Mycobacterium for this purpose is Bacillus Calmette-Guerin (BCG), an avirulent strain of *Mycobacterium bovis*. However, the safety and efficacy of BCG is a source of controversy and some countries, such as the United States, do not vaccinate the general public. Diagnosis is commonly achieved using a skin test, which involves intradermal exposure to tuberculin PPD (protein-purified derivative). Antigen-specific T cell responses result in measurable incubation at the injection site by 48-72 hours after injection, which indicates exposure to Mycobacterial antigens. Sensitivity and specificity have, however, been a problem with this test, and individuals vaccinated with BCG cannot be distinguished from infected individuals.

While macrophages have been shown to act as the principal effectors of *M. tuberculosis* immunity, T cells are the predominant inducers of such immunity. The essential role of T cells in protection against *M. tuberculosis* infection is illustrated by the frequent occurrence of *M. tuberculosis* in AIDS patients, due to the depletion of CD4 T cells associated with human immunodeficiency virus (HIV) infection. Mycobacterium-reactive CD4 T cells have been shown to be potent producers of gamma-interferon (IFN- $\gamma$ ), which, in turn, has been shown to trigger the anti-mycobacterial effects of macrophages in mice. While the role of IFN- $\gamma$  in humans is less clear, studies have shown that 1,25-dihydroxy-vitamin D3, either alone or in combination with IFN- $\gamma$  or tumor necrosis factor-alpha, activates human macrophages to inhibit *M. tuberculosis* infection. Furthermore, it is known that IFN- $\gamma$  stimulates human macrophages to make 1,25-dihydroxy-vitamin D3. Similarly, IL-12 has been shown to play a role in stimulating resistance to *M. tuberculosis* infection. For a review



*Tuberculosis: Pathogenesis, Protection and Control*, Bloom (ed.), ASM Press, Washington, DC, 1994.

Accordingly, there is a need in the art for improved diagnostic methods for detecting tuberculosis. The present invention fulfills this need and further provides  
 5 other related advantages.

#### Summary of the Invention

Briefly stated, the present invention provides compositions and methods for diagnosing tuberculosis. In one aspect, polypeptides are provided comprising an  
 10 antigenic portion of a soluble *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications. In one embodiment of this aspect, the soluble antigen has one of the following N-terminal sequences:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu (SEQ ID No. 115);
- 15 (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser (SEQ ID No. 116);
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg (SEQ ID No. 117);
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro (SEQ ID No. 118);
- 20 (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val (SEQ ID No. 119);
- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro (SEQ ID No. 120);
- 25 (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Thr-Ala-Ala-Ser-Pro-Pro-Ser (SEQ ID No. 121);
- (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly (SEQ ID No. 122)

- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn (SEQ ID No. 123);
- (j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 129)
- (k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 130) or
- (l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 131)

wherein Xaa may be any amino acid.

In a related aspect, polypeptides are provided comprising an immunogenic portion of an *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications, the antigen having one of the following N-terminal sequences:

- (m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 132) or
- (n) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 124)

wherein Xaa may be any amino acid.

In another embodiment, the antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos. 1, 2, 4-10, 13-25, 52, 94 and 96, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos. 1, 2, 4-10, 13-25, 52, 94 and 96 or a complement thereof under moderately stringent conditions.

In a related aspect, the polypeptides comprise an antigenic portion of a *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative

sequences recited in SEQ ID Nos. 26-51, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos. 26-51 or a complement thereof under moderately stringent conditions.

In related aspects, DNA sequences encoding the above polypeptides, 5 recombinant expression vectors comprising these DNA sequences and host cells transformed or transfected with such expression vectors are also provided.

In another aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, an inventive polypeptide and a known *M. tuberculosis* antigen.

10 In further aspects of the subject invention, methods and diagnostic kits are provided for detecting tuberculosis in a patient. The methods comprise: (a) contacting a biological sample with at least one of the above polypeptides; and (b) detecting in the sample the presence of antibodies that bind to the polypeptide or polypeptides, thereby detecting *M. tuberculosis* infection in the biological sample. 15 Suitable biological samples include whole blood, sputum, serum, plasma, saliva, cerebrospinal fluid and urine. The diagnostic kits comprise one or more of the above polypeptides in combination with a detection reagent.

The present invention also provides methods for detecting *M. tuberculosis* infection comprising: (a) obtaining a biological sample from a patient; 20 (b) contacting the sample with a first and a second oligonucleotide primer in a polymerase chain reaction, the first and the second oligonucleotide primers comprising at least about 10 contiguous nucleotides of a DNA sequence encoding the above polypeptides; and (c) detecting in the sample a DNA sequence that amplifies in the presence of the first and second oligonucleotide primers.

25 In a further aspect, the present invention provides a method for detecting *M. tuberculosis* infection in a patient comprising: (a) obtaining a biological sample from the patient; (b) contacting the sample with an oligonucleotide probe comprising at least about 15 contiguous nucleotides of a DNA sequence encoding the above

In yet another aspect, the present invention provides antibodies, both polyclonal and monoclonal, that bind to the polypeptides described above, as well as methods for their use in the detection of *M. tuberculosis* infection.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

#### Brief Description of the Drawings and Sequence Identifiers

Figure 1A and B illustrate the stimulation of proliferation and interferon- $\gamma$  production in T cells derived from a first and a second *M. tuberculosis*-immune donor, respectively, by the 14 Kd, 20 Kd and 26 Kd antigens described in Example 1.

Figure 2 illustrates the reactivity of two representative polypeptides with sera from *M. tuberculosis*-infected and uninfected individuals, as compared to the reactivity of bacterial lysate.

Figure 3 shows the reactivity of four representative polypeptides with sera from *M. tuberculosis*-infected and uninfected individuals, as compared to the reactivity of the 38 kD antigen.

Figure 4 shows the reactivity of recombinant 38 kD and TbRa11 antigens with sera from *M. tuberculosis* patients, PPD positive donors and normal donors.

Figure 5 shows the reactivity of the antigen TbRa2A with 38 kD negative sera.

Figure 6 shows the reactivity of the antigen of SEQ ID No. 60 with sera from *M. tuberculosis* patients and normal donors.

SEQ. ID NO. 1 is the DNA sequence of TbRa1.

SEQ. ID NO. 2 is the DNA sequence of TbRa10.

SEQ. ID NO. 3 is the DNA sequence of TbRa11.

- SEQ. ID NO. 7 is the DNA sequence of TbRa17.  
SEQ. ID NO. 8 is the DNA sequence of TbRa18.  
SEQ. ID NO. 9 is the DNA sequence of TbRa19.  
SEQ. ID NO. 10 is the DNA sequence of TbRa24.  
5 SEQ. ID NO. 11 is the DNA sequence of TbRa26.  
SEQ. ID NO. 12 is the DNA sequence of TbRa28.  
SEQ. ID NO. 13 is the DNA sequence of TbRa29.  
SEQ. ID NO. 14 is the DNA sequence of TbRa2A.  
SEQ. ID NO. 15 is the DNA sequence of TbRa3.  
10 SEQ. ID NO. 16 is the DNA sequence of TbRa32.  
SEQ. ID NO. 17 is the DNA sequence of TbRa35.  
SEQ. ID NO. 18 is the DNA sequence of TbRa36.  
SEQ. ID NO. 19 is the DNA sequence of TbRa4.  
SEQ. ID NO. 20 is the DNA sequence of TbRa9.  
15 SEQ. ID NO. 21 is the DNA sequence of TbRaB.  
SEQ. ID NO. 22 is the DNA sequence of TbRaC.  
SEQ. ID NO. 23 is the DNA sequence of TbRaD.  
SEQ. ID NO. 24 is the DNA sequence of YYWCPG.  
SEQ. ID NO. 25 is the DNA sequence of AAMK.  
20 SEQ. ID NO. 26 is the DNA sequence of TbL-23.  
SEQ. ID NO. 27 is the DNA sequence of TbL-24.  
SEQ. ID NO. 28 is the DNA sequence of TbL-25.  
SEQ. ID NO. 29 is the DNA sequence of TbL-28.  
SEQ. ID NO. 30 is the DNA sequence of TbL-29.  
25 SEQ. ID NO. 31 is the DNA sequence of TbH-5.  
SEQ. ID NO. 32 is the DNA sequence of TbH-8.  
SEQ. ID NO. 33 is the DNA sequence of TbH-9.  
SEQ. ID NO. 34 is the DNA sequence of TbM-1.  
SEQ. ID NO. 35 is the DNA sequence of TbM-3.  
30 SEQ. ID NO. 36 is the DNA sequence of TbM-6.  
SEQ. ID NO. 37 is the DNA sequence of TbM-7.  
SEQ. ID NO. 38 is the DNA sequence of TbM-9.  
SEQ. ID NO. 39 is the DNA sequence of TbM-12.

- SEQ. ID NO. 43 is the DNA sequence of TbH-4.
- SEQ. ID NO. 44 is the DNA sequence of TbH-4-FWD.
- SEQ. ID NO. 45 is the DNA sequence of TbH-12.
- SEQ. ID NO. 46 is the DNA sequence of Tb38-1.
- 5 SEQ. ID NO. 47 is the DNA sequence of Tb38-4.
- SEQ. ID NO. 48 is the DNA sequence of TbL-17.
- SEQ. ID NO. 49 is the DNA sequence of TbL-20.
- SEQ. ID NO. 50 is the DNA sequence of TbL-21.
- SEQ. ID NO. 51 is the DNA sequence of TbH-16.
- 10 SEQ. ID NO. 52 is the DNA sequence of DPEP.
- SEQ. ID NO. 53 is the deduced amino acid sequence of DPEP.
- SEQ. ID NO. 54 is the protein sequence of DPV N-terminal Antigen.
- SEQ. ID NO. 55 is the protein sequence of AVGS N-terminal Antigen.
- SEQ. ID NO. 56 is the protein sequence of AAMK N-terminal Antigen.
- 15 SEQ. ID NO. 57 is the protein sequence of YYWC N-terminal Antigen.
- SEQ. ID NO. 58 is the protein sequence of DIGS N-terminal Antigen.
- SEQ. ID NO. 59 is the protein sequence of AEES N-terminal Antigen.
- SEQ. ID NO. 60 is the protein sequence of DPEP N-terminal Antigen.
- SEQ. ID NO. 61 is the protein sequence of APKT N-terminal Antigen.
- 20 SEQ. ID NO. 62 is the protein sequence of DPAS N-terminal Antigen.
- SEQ. ID NO. 63 is the deduced amino acid sequence of TbM-1 Peptide.
- SEQ. ID NO. 64 is the deduced amino acid sequence of TbRa1.
- SEQ. ID NO. 65 is the deduced amino acid sequence of TbRa10.
- SEQ. ID NO. 66 is the deduced amino acid sequence of TbRa11.
- 25 SEQ. ID NO. 67 is the deduced amino acid sequence of TbRa12.
- SEQ. ID NO. 68 is the deduced amino acid sequence of TbRa13.
- SEQ. ID NO. 69 is the deduced amino acid sequence of TbRa16.
- SEQ. ID NO. 70 is the deduced amino acid sequence of TbRa17.
- SEQ. ID NO. 71 is the deduced amino acid sequence of TbRa18.
- 30 SEQ. ID NO. 72 is the deduced amino acid sequence of TbRa19.
- SEQ. ID NO. 73 is the deduced amino acid sequence of TbRa24.
- SEQ. ID NO. 74 is the deduced amino acid sequence of TbRa26.
- SEQ. ID NO. 75 is the deduced amino acid sequence of TbRa28.

- SEQ. ID NO. 79 is the deduced amino acid sequence of TbRa32.  
SEQ. ID NO. 80 is the deduced amino acid sequence of TbRa35.  
SEQ. ID NO. 81 is the deduced amino acid sequence of TbRa36.  
SEQ. ID NO. 82 is the deduced amino acid sequence of TbRa4.  
5 SEQ. ID NO. 83 is the deduced amino acid sequence of TbRa9.  
SEQ. ID NO. 84 is the deduced amino acid sequence of TbRaB.  
SEQ. ID NO. 85 is the deduced amino acid sequence of TbRaC.  
SEQ. ID NO. 86 is the deduced amino acid sequence of TbRaD.  
SEQ. ID NO. 87 is the deduced amino acid sequence of YYWCPG.  
10 SEQ. ID NO. 88 is the deduced amino acid sequence of TbAAMK.  
SEQ. ID NO. 89 is the deduced amino acid sequence of Tb38-1.  
SEQ. ID NO. 90 is the deduced amino acid sequence of TbH-4.  
SEQ. ID NO. 91 is the deduced amino acid sequence of TbH-8.  
SEQ. ID NO. 92 is the deduced amino acid sequence of TbH-9.  
15 SEQ. ID NO. 93 is the deduced amino acid sequence of TbH-12.  
SEQ. ID NO. 94 is the DNA sequence of DPAS.  
SEQ. ID NO. 95 is the deduced amino acid sequence of DPAS.  
SEQ. ID NO. 96 is the DNA sequence of DPV.  
SEQ. ID NO. 97 is the deduced amino acid sequence of DPV.  
20 SEQ. ID NO. 98 is the DNA sequence of ESAT-6.  
SEQ. ID NO. 99 is the deduced amino acid sequence of ESAT-6.  
SEQ. ID NO. 100 is the DNA sequence of TbH-8-2.  
SEQ. ID NO. 101 is the DNA sequence of TbH-9FL.  
SEQ. ID NO. 102 is the deduced amino acid sequence of TbH-9FL.  
25 SEQ. ID NO. 103 is the DNA sequence of TbH-9-1.  
SEQ. ID NO. 104 is the deduced amino acid sequence of TbH-9-1.  
SEQ. ID NO. 105 is the DNA sequence of TbH-9-4.  
SEQ. ID NO. 106 is the deduced amino acid sequence of TbH-9-4.  
SEQ. ID NO. 107 is the DNA sequence of Tb38-1F2 IN.  
30 SEQ. ID NO. 108 is the DNA sequence of Tb38-1F2 RP.  
SEQ. ID NO. 109 is the deduced amino acid sequence of Tb37-FL.  
SEQ. ID NO. 110 is the deduced amino acid sequence of Tb38-IN.  
SEQ. ID NO. 111 is the DNA sequence of Tb38-1F3.

- SEQ. ID NO. 115 is the deduced N-terminal amino acid sequence of DPV.  
SEQ. ID NO. 116 is the deduced N-terminal amino acid sequence of AVGS.  
SEQ. ID NO. 117 is the deduced N-terminal amino acid sequence of AAMK.  
SEQ. ID NO. 118 is the deduced N-terminal amino acid sequence of YYWC.  
5 SEQ. ID NO. 119 is the deduced N-terminal amino acid sequence of DIGS.  
SEQ. ID NO. 120 is the deduced N-terminal amino acid sequence of AAES.  
SEQ. ID NO. 121 is the deduced N-terminal amino acid sequence of DPEP.  
SEQ. ID NO. 122 is the deduced N-terminal amino acid sequence of APKT.  
SEQ. ID NO. 123 is the deduced N-terminal amino acid sequence of DPAS.  
10 SEQ. ID NO. 124 is the protein sequence of DPPD N-terminal Antigen.  
SEQ ID NO. 125-128 are the protein sequences of four DPPD cyanogen  
bromide fragments.  
SEQ ID NO. 129 is the N-terminal protein sequence of XDS antigen.  
SEQ ID NO. 130 is the N-terminal protein sequence of AGD antigen.  
15 SEQ ID NO. 131 is the N-terminal protein sequence of APE antigen.  
SEQ ID NO. 132 is the N-terminal protein sequence of XYI antigen.

#### Detailed Description of the Invention

- 20 As noted above, the present invention is generally directed to compositions and methods for diagnosing tuberculosis. The compositions of the subject invention include polypeptides that comprise at least one antigenic portion of a *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications. Polypeptides within the scope of the present  
25 invention include, but are not limited to, soluble *M. tuberculosis* antigens. A "soluble *M. tuberculosis* antigen" is a protein of *M. tuberculosis* origin that is present in *M. tuberculosis* culture filtrate. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins (*i.e.*, antigens), wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide  
30 comprising an antigenic portion of one of the above antigens may consist entirely of the antigenic portion, or may contain additional sequences. The additional sequences



An "antigenic portion" of an antigen (which may or may not be soluble) is a portion that is capable of reacting with sera obtained from an *M. tuberculosis*-infected individual (i.e., generates an absorbance reading with sera from infected individuals that is at least three standard deviations above the absorbance obtained with sera from uninfected individuals, in a representative ELISA assay described herein). An "*M. tuberculosis*-infected individual" is a human who has been infected with *M. tuberculosis* (e.g., has an intradermal skin test response to PPD that is at least 0.5 cm in diameter). Infected individuals may display symptoms of tuberculosis or may be free of disease symptoms. Polypeptides comprising at least an antigenic portion of one or more *M. tuberculosis* antigens as described herein may generally be used, alone or in combination, to detect tuberculosis in a patient.

The compositions and methods of this invention also encompass variants of the above polypeptides. A "variant," as used herein, is a polypeptide that differs from the native antigen only in conservative substitutions and/or modifications, such that the antigenic properties of the polypeptide are retained. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the antigenic properties of the modified polypeptide using, for example, the representative procedures described herein.

A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. In general, the following groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the antigenic properties, secondary structure and hydrophobic nature of the polypeptide.

protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

5 In a related aspect, combination polypeptides are disclosed. A "combination polypeptide" is a polypeptide comprising at least one of the above antigenic portions and one or more additional antigenic *M. tuberculosis* sequences, which are joined via a peptide linkage into a single amino acid chain. The sequences may be joined directly (i.e., with no intervening amino acids) or may be joined by way  
10 of a linker sequence (e.g., Gly-Cys-Gly) that does not significantly diminish the antigenic properties of the component polypeptides.

In general, *M. tuberculosis* antigens, and DNA sequences encoding such antigens, may be prepared using any of a variety of procedures. For example, soluble antigens may be isolated from *M. tuberculosis* culture filtrate by procedures known to  
15 those of ordinary skill in the art, including anion-exchange and reverse phase chromatography. Purified antigens may then be evaluated for a desired property, such as the ability to react with sera obtained from an *M. tuberculosis*-infected individual. Such screens may be performed using the representative methods described herein. Antigens may then be partially sequenced using, for example, traditional Edman  
20 chemistry. See Edman and Berg, *Eur. J. Biochem.* 80:116-132, 1967.

Antigens may also be produced recombinantly using a DNA sequence that encodes the antigen, which has been inserted into an expression vector and expressed in an appropriate host. DNA molecules encoding soluble antigens may be isolated by screening an appropriate *M. tuberculosis* expression library with anti-sera  
25 (e.g., rabbit) raised specifically against soluble *M. tuberculosis* antigens. DNA sequences encoding antigens that may or may not be soluble may be identified by screening an appropriate *M. tuberculosis* genomic or cDNA expression library with sera obtained from patients infected with *M. tuberculosis*. Such screens may generally be

et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989.

DNA sequences encoding soluble antigens may also be obtained by screening an appropriate *M. tuberculosis* cDNA or genomic DNA library for DNA sequences that hybridize to degenerate oligonucleotides derived from partial amino acid sequences of isolated soluble antigens. Degenerate oligonucleotide sequences for use in such a screen may be designed and synthesized, and the screen may be performed, as described (for example) in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY (and references cited therein). Polymerase chain reaction (PCR) may also be employed, using the above oligonucleotides in methods well known in the art, to isolate a nucleic acid probe from a cDNA or genomic library. The library screen may then be performed using the isolated probe.

Regardless of the method of preparation, the antigens described herein are "antigenic." More specifically, the antigens have the ability to react with sera obtained from an *M. tuberculosis*-infected individual. Reactivity may be evaluated using, for example, the representative ELISA assays described herein, where an absorbance reading with sera from infected individuals that is at least three standard deviations above the absorbance obtained with sera from uninfected individuals is considered positive.

Antigenic portions of *M. tuberculosis* antigens may be prepared and identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3d ed., Raven Press, 1993, pp. 243-247 and references cited therein. Such techniques include screening polypeptide portions of the native antigen for antigenic properties. The representative ELISAs described herein may generally be employed in these screens. An antigenic portion of a polypeptide is a portion that, within such representative assays, generates a signal in such assays that is substantially similar to that generated by the full length antigen. In other words, an antigenic portion

Portions and other variants of *M. tuberculosis* antigens may be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc., Foster City, CA, and may be operated according to the manufacturer's instructions. Variants of a native antigen may generally be prepared using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis. Sections of the DNA sequence may also be removed using standard techniques to permit preparation of truncated polypeptides.

Recombinant polypeptides containing portions and/or variants of a native antigen may be readily prepared from a DNA sequence encoding the polypeptide using a variety of techniques well known to those of ordinary skill in the art. For example, supernatants from suitable host/vector systems which secrete recombinant protein into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant protein.

Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides as described herein. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian

encode naturally occurring antigens, portions of naturally occurring antigens, or other variants thereof.

In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in substantially pure form. Preferably, the polypeptides  
5 are at least about 80% pure, more preferably at least about 90% pure and most preferably at least about 99% pure. For use in the methods described herein, however, such substantially pure polypeptides may be combined.

In certain specific embodiments, the subject invention discloses polypeptides comprising at least an antigenic portion of a soluble *M. tuberculosis*  
10 antigen (or a variant of such an antigen), where the antigen has one of the following N-terminal sequences:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu (SEQ ID No. 115);
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser (SEQ ID No. 116);
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg (SEQ ID No. 117);
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro (SEQ ID No. 118);
- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val (SEQ ID No. 119);
- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro (SEQ ID No. 120);
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Thr-Ala-Ala-Ser-Pro-Pro-Ser (SEQ ID No. 121);
- (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly (SEQ ID No. 122);
- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gly-Gln

- (j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 129)
- (k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 130) or
- 5 (l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 131)

wherein Xaa may be any amino acid, preferably a cysteine residue. A DNA sequence encoding the antigen identified as (g) above is provided in SEQ ID No. 52, the deduced amino acid sequence of which is provided in SEQ ID No. 53. A DNA sequence encoding the antigen identified as (a) above is provided in SEQ ID No. 96; its deduced amino acid sequence is provided in SEQ ID No. 97. A DNA sequence corresponding to antigen (d) above is provided in SEQ ID No. 24, a DNA sequence corresponding to antigen (c) is provided in SEQ ID No. 25 and a DNA sequence corresponding to antigen (l) is disclosed in SEQ ID No. 94 and its deduced amino acid sequence is provided in

10

15 SEQ ID No. 95.

In a further specific embodiment, the subject invention discloses polypeptides comprising at least an immunogenic portion of an *M. tuberculosis* antigen having one of the following N-terminal sequences, or a variant thereof that differs only in conservative substitutions and/or modifications:

- 20 (m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 132) or
- (n) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 124)

25 wherein Xaa may be any amino acid, preferably a cysteine residue.

In other specific embodiments, the subject invention discloses polypeptides comprising at least an antigenic portion of a soluble *M. tuberculosis* antigen (or a variant of such an antigen) that comprises one or more of the amino acid

and 96, (b) the complements of such DNA sequences, or (c) DNA sequences substantially homologous to a sequence in (a) or (b).

In further specific embodiments, the subject invention discloses polypeptides comprising at least an antigenic portion of a *M. tuberculosis* antigen (or a variant of such an antigen), which may or may not be soluble, that comprises one or more of the amino acid sequences encoded by (a) the DNA sequences of SEQ ID Nos. 26-51, (b) the complements of such DNA sequences or (c) DNA sequences substantially homologous to a sequence in (a) or (b).

In the specific embodiments discussed above, the *M. tuberculosis* antigens include variants that are encoded DNA sequences which are substantially homologous to one or more of DNA sequences specifically recited herein. "Substantial homology," as used herein, refers to DNA sequences that are capable of hybridizing under moderately stringent conditions. Suitable moderately stringent conditions include prewashing in a solution of 5X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5X SSC, overnight or, in the event of cross-species homology, at 45°C with 0.5X SSC; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS). Such hybridizing DNA sequences are also within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing DNA sequence.

In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of the present invention and a known *M. tuberculosis* antigen, such as the 38 kD antigen described above or ESAT-6 (SEQ ID Nos. 98 and 99), together with variants of such fusion proteins. The fusion proteins of the present invention may also include a linker peptide between the first and second polypeptides.

A DNA sequence encoding a fusion protein of the present invention is constructed using known recombinant DNA techniques to assemble

without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide so that the reading frames of the sequences are in phase to permit mRNA translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

5 A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to  
10 adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the  
15 linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA* 83:8258-8562, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide linker sequences are not required when the first and second polypeptides have  
20 non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric hindrance.

In another aspect, the present invention provides methods for using the polypeptides described above to diagnose tuberculosis. In this aspect, methods are provided for detecting *M. tuberculosis* infection in a biological sample, using one or  
25 more of the above polypeptides, alone or in combination. In embodiments in which multiple polypeptides are employed, polypeptides other than those specifically described herein, such as the 38 kD antigen described in Andersen and Hansen, *Infect. Immun.* 57:2481-2488, 1989, may be included. As used herein, a "biological sample" is



preferably, the sample is a blood, serum or plasma sample obtained from a patient or a blood supply. The polypeptide(s) are used in an assay, as described below, to determine the presence or absence of antibodies to the polypeptide(s) in the sample, relative to a predetermined cut-off value. The presence of such antibodies indicates previous sensitization to mycobacteria antigens which may be indicative of tuberculosis.

In embodiments in which more than one polypeptide is employed, the polypeptides used are preferably complementary (*i.e.*, one component polypeptide will tend to detect infection in samples where the infection would not be detected by another component polypeptide). Complementary polypeptides may generally be identified by using each polypeptide individually to evaluate serum samples obtained from a series of patients known to be infected with *M. tuberculosis*. After determining which samples test positive (as described below) with each polypeptide, combinations of two or more polypeptides may be formulated that are capable of detecting infection in most or all, of the samples tested. Such polypeptides are complementary. For example, approximately 25-30% of sera from tuberculosis-infected individuals are negative for antibodies to any single protein, such as the 38 kD antigen mentioned above. Complementary polypeptides may, therefore, be used in combination with the 38 kD antigen to improve sensitivity of a diagnostic test.

There are a variety of assay formats known to those of ordinary skill in the art for using one or more polypeptides to detect antibodies in a sample. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988, which is incorporated herein by reference. In a preferred embodiment, the assay involves the use of polypeptide immobilized on a solid support to bind to and remove the antibody from the sample. The bound antibody may then be detected using a detection reagent that contains a reporter group. Suitable detection reagents include antibodies that bind to the antibody/polypeptide complex and free polypeptide labeled with a reporter group (*e.g.*, in a semi-competitive assay). Alternatively, a competitive assay may be utilized, in which an antibody that binds to the polypeptide is labeled.

binding of the labeled antibody to the polypeptide is indicative of the reactivity of the sample with the immobilized polypeptide.

The solid support may be any solid material known to those of ordinary skill in the art to which the antigen may be attached. For example, the solid support  
5 may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681.

10 The polypeptides may be bound to the solid support using a variety of techniques known to those of ordinary skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "bound" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the antigen and functional groups on the  
15 support or may be a linkage by way of a cross-linking agent). Binding by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the polypeptide, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and 1 day. In general, contacting a well of a plastic microtiter  
20 plate (such as polystyrene or polyvinylchloride) with an amount of polypeptide ranging from about 10 ng to about 1  $\mu$ g, and preferably about 100 ng, is sufficient to bind an adequate amount of antigen.

Covalent attachment of polypeptide to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with  
25 both the support and a functional group, such as a hydroxyl or amino group, on the polypeptide. For example, the polypeptide may be bound to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the polypeptide.

In certain embodiments, the assay is an enzyme linked immunosorbent assay (ELISA). This assay may be performed by first contacting a polypeptide antigen that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that antibodies to the polypeptide within the sample are allowed  
5 to bind to the immobilized polypeptide. Unbound sample is then removed from the immobilized polypeptide and a detection reagent capable of binding to the immobilized antibody-polypeptide complex is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific detection reagent.

10 More specifically, once the polypeptide is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO) may be employed. The immobilized polypeptide is then incubated with the sample, and  
15 antibody is allowed to bind to the antigen. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is that period of time that is sufficient to detect the presence of antibody within a *M. tuberculosis*-infected sample. Preferably, the contact time is sufficient to achieve a level of binding that is at least 95% of that  
20 achieved at equilibrium between bound and unbound antibody. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support  
25 with an appropriate buffer, such as PBS containing 0.1% Tween 20™. Detection reagent may then be added to the solid support. An appropriate detection reagent is any compound that binds to the immobilized antibody-polypeptide complex and that can be detected by any of a variety of means known to those in the art.

reporter groups include enzymes (such as horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. The conjugation of binding agent to reporter group may be achieved using standard methods known to those of ordinary skill in the art. Common binding agents may also be  
5 purchased conjugated to a variety of reporter groups from many commercial sources (e.g., Zymed Laboratories, San Francisco, CA, and Pierce, Rockford, IL).

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound antibody. An appropriate amount of time may generally be determined from the manufacturer's  
10 instructions or by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic  
15 methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

20 To determine the presence or absence of anti-*M. tuberculosis* antibodies in the sample, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value is the average mean signal obtained when the immobilized antigen is incubated with samples from an uninfected  
25 patient. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for tuberculosis. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al. *Clinical Epidemiology & Biostatistics* 4: 307-313 (1980).

rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for tuberculosis.

10 In a related embodiment, the assay is performed in a rapid flow-through or strip test format, wherein the antigen is immobilized on a membrane, such as nitrocellulose. In the flow-through test, antibodies within the sample bind to the immobilized polypeptide as the sample passes through the membrane. A detection reagent (*e.g.*, protein A-colloidal gold) then binds to the antibody-polypeptide complex as the solution containing the detection reagent flows through the membrane. The detection of bound detection reagent may then be performed as described above. In the strip test format, one end of the membrane to which polypeptide is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing detection reagent and to the area of immobilized polypeptide. Concentration of detection reagent at the polypeptide indicates the presence of anti-*M. tuberculosis* antibodies in the sample. Typically, the concentration of detection reagent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of polypeptide immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of antibodies that would be sufficient to generate a positive signal in an ELISA, as discussed above. Preferably, the amount of polypeptide immobilized on the membrane ranges from about 25 ng to about 1 µg, and more preferably from about 50 ng to about 500 ng.

Of course, numerous other assay protocols exist that are suitable for use with the polypeptides of the present invention. The above descriptions are intended to be exemplary only.

In yet another aspect, the present invention provides antibodies to the inventive polypeptides. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In one such technique, an immunogen comprising the antigenic polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep and goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for the antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of fused cells.

colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Antibodies may be used in diagnostic tests to detect the presence of *M. tuberculosis* antigens using assays similar to those detailed above and other techniques well known to those of skill in the art, thereby providing a method for detecting *M. tuberculosis* infection in a patient.

Diagnostic reagents of the present invention may also comprise DNA sequences encoding one or more of the above polypeptides, or one or more portions thereof. For example, primers comprising at least 10 contiguous oligonucleotides of the subject DNA sequences may be used in polymerase chain reaction (PCR) based tests. Similarly, probes comprising at least 15 contiguous oligonucleotides of the subject DNA sequences may be used for hybridizing to specific sequences. Techniques for both PCR based tests and hybridization tests are well known in the art. Primers or probes may thus be used to detect *M. tuberculosis* infection in biological samples, preferably sputum, blood, serum, saliva, cerebrospinal fluid or urine. DNA probes or primers comprising oligonucleotide sequences described above may be used alone, in combination with each other, or with previously identified sequences, such as the 38 kD antigen discussed above.

## EXAMPLES

### EXAMPLE 1

5                    PURIFICATION AND CHARACTERIZATION OF POLYPEPTIDES  
                    FROM *M. TUBERCULOSIS* CULTURE FILTRATE

This example illustrates the preparation of *M. tuberculosis* soluble polypeptides from culture filtrate. Unless otherwise noted, all percentages in the  
10 following example are weight per volume.

*M. tuberculosis* (either H37Ra, ATCC No. 25177, or H37Rv, ATCC No. 25618) was cultured in sterile GAS media at 37°C for fourteen days. The media was then vacuum filtered (leaving the bulk of the cells) through a 0.45  $\mu$  filter into a sterile 2.5 L bottle. The media was then filtered through a 0.2  $\mu$  filter into a sterile 4 L  
15 bottle.  $\text{NaN}_3$  was then added to the culture filtrate to a concentration of 0.04%. The bottles were then placed in a 4°C cold room.

The culture filtrate was concentrated by placing the filtrate in a 12 L reservoir that had been autoclaved and feeding the filtrate into a 400 ml Amicon stir cell which had been rinsed with ethanol and contained a 10,000 kDa MWCO membrane.  
20 The pressure was maintained at 60 psi using nitrogen gas. This procedure reduced the 12 L volume to approximately 50 ml.

The culture filtrate was then dialyzed into 0.1% ammonium bicarbonate using a 8,000 kDa MWCO cellulose ester membrane, with two changes of ammonium bicarbonate solution. Protein concentration was then determined by a commercially  
25 available BCA assay (Pierce, Rockford, IL).

The dialyzed culture filtrate was then lyophilized, and the polypeptides resuspended in distilled water. The polypeptides were then dialyzed against 0.01 mM 1,3 bis[tris(hydroxymethyl)-methylamino]propane, pH 7.5 (Bio-Tek, Boston, MA).



4.6 mm x 100 mm (Perseptive BioSystems, Framingham, MA) equilibrated in 0.01 mM Bis-Tris propane buffer pH 7.5. Polypeptides were eluted with a linear 0-0.5 M NaCl gradient in the above buffer system. The column eluent was monitored at a wavelength of 220 nm.

5           The pools of polypeptides eluting from the ion exchange column were dialyzed against distilled water and lyophilized. The resulting material was dissolved in 0.1% trifluoroacetic acid (TFA) pH 1.9 in water, and the polypeptides were purified on a Delta-Pak C18 column (Waters, Milford, MA) 300 Angstrom pore size, 5 micron particle size (3.9 x 150 mm). The polypeptides were eluted from the column with a  
10 linear gradient from 0-60% dilution buffer (0.1% TFA in acetonitrile). The flow rate was 0.75 ml/minute and the HPLC eluent was monitored at 214 nm. Fractions containing the eluted polypeptides were collected to maximize the purity of the individual samples. Approximately 200 purified polypeptides were obtained.

          The purified polypeptides were then screened for the ability to induce T-  
15 cell proliferation in PBMC preparations. The PBMCs from donors known to be PPD skin test positive and whose T cells were shown to proliferate in response to PPD and crude soluble proteins from MTB were cultured in medium comprising RPMI 1640 supplemented with 10% pooled human serum and 50 µg/ml gentamicin. Purified polypeptides were added in duplicate at concentrations of 0.5 to 10 µg/mL. After six  
20 days of culture in 96-well round-bottom plates in a volume of 200 µl, 50 µl of medium was removed from each well for determination of IFN-γ levels, as described below. The plates were then pulsed with 1 µCi/well of tritiated thymidine for a further 18 hours, harvested and tritium uptake determined using a gas scintillation counter. Fractions that resulted in proliferation in both replicates three fold greater than the  
25 proliferation observed in cells cultured in medium alone were considered positive.

          IFN-γ was measured using an enzyme-linked immunosorbent assay (ELISA). ELISA plates were coated with a mouse monoclonal antibody directed to

superantigen. Plates were then washed three times in PBS containing 0.1% TWEEEN-20 and

samples diluted 1:2 in culture medium in the ELISA plates were incubated overnight at room temperature. The plates were again washed and a polyclonal rabbit anti-human IFN- $\gamma$  serum diluted 1:3000 in PBS/10% normal goat serum was added to each well. The plates were then incubated for two hours at room temperature, washed and  
5 horseradish peroxidase-coupled anti-rabbit IgG (Jackson Labs.) was added at a 1:2000 dilution in PBS/5% non-fat dried milk. After a further two hour incubation at room temperature, the plates were washed and TMB substrate added. The reaction was stopped after 20 min with 1 N sulfuric acid. Optical density was determined at 450 nm using 570 nm as a reference wavelength. Fractions that resulted in both replicates,  
10 giving an OD two fold greater than the mean OD from cells cultured in medium alone, plus 3 standard deviations, were considered positive.

For sequencing, the polypeptides were individually dried onto Biobrene™ (Perkin Elmer/Applied BioSystems Division, Foster City, CA) treated glass fiber filters. The filters with polypeptide were loaded onto a Perkin Elmer/Applied  
15 BioSystems Division Procise 492 protein sequencer. The polypeptides were sequenced from the amino terminal and using traditional Edman chemistry. The amino acid sequence was determined for each polypeptide by comparing the retention time of the PTH amino acid derivative to the appropriate PTH derivative standards.

Using the procedure described above, antigens having the following  
20 N-terminal sequences were isolated:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Xaa-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu (SEQ ID No. 54);
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser (SEQ ID No. 55);
- 25 (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg (SEQ ID No. 56);
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Irp-Gly-Pro (SEQ ID No. 57)

- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro (SEQ ID No. 59);
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Ala-Ala-Ala-Ala-Pro-Pro-Ala (SEQ ID No. 60); and
- 5 (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly (SEQ ID No. 61);

wherein Xaa may be any amino acid.

An additional antigen was isolated employing a microbore HPLC purification step in addition to the procedure described above. Specifically, 20  $\mu$ l of a  
10 fraction comprising a mixture of antigens from the chromatographic purification step previously described, was purified on an Aquapore C18 column (Perkin Elmer/Applied Biosystems Division, Foster City, CA) with a 7 micron pore size, column size 1 mm x 100 mm, in a Perkin Elmer/Applied Biosystems Division Model 172 HPLC. Fractions were eluted from the column with a linear gradient of 1%/minute of acetonitrile  
15 (containing 0.05% TFA) in water (0.05% TFA) at a flow rate of 80  $\mu$ l/minute. The eluent was monitored at 250 nm. The original fraction was separated into 4 major peaks plus other smaller components and a polypeptide was obtained which was shown to have a molecular weight of 12.054 Kd (by mass spectrometry) and the following N-terminal sequence:

- 20 (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Gln-Thr-Ser-Leu-Leu-Asn-Asn-Leu-Ala-Asp-Pro-Asp-Val-Ser-Phe-Ala-Asp (SEQ ID No. 62).

This polypeptide was shown to induce proliferation and IFN- $\gamma$  production in PBMC preparations using the assays described above.

25 Additional soluble antigens were isolated from *M. tuberculosis* culture filtrate as follows. *M. tuberculosis* culture filtrate was prepared as described above. Following dialysis against Bis-Tris propane buffer, at pH 5.5, fractionation was performed using anion exchange chromatography on a Poros QF column 4.6 x 100 mm.

were eluted with a linear 0-1.5 M NaCl gradient in the above buffer system at a flow rate of 10 ml/min. The column eluent was monitored at a wavelength of 214 nm.

The fractions eluting from the ion exchange column were pooled and subjected to reverse phase chromatography using a Poros R2 column 4.6 x 100 mm (Perseptive Biosystems). Polypeptides were eluted from the column with a linear gradient from 0-100% acetonitrile (0.1% TFA) at a flow rate of 5 ml/min. The eluent was monitored at 214 nm.

Fractions containing the eluted polypeptides were lyophilized and resuspended in 80 µl of aqueous 0.1% TFA and further subjected to reverse phase chromatography on a Vydac C4 column 4.6 x 150 mm (Western Analytical, Temecula, CA) with a linear gradient of 0-100% acetonitrile (0.1% TFA) at a flow rate of 2 ml/min. Eluent was monitored at 214 nm.

The fraction with biological activity was separated into one major peak plus other smaller components. Western blot of this peak onto PVDF membrane revealed three major bands of molecular weights 14 Kd, 20 Kd and 26 Kd. These polypeptides were determined to have the following N-terminal sequences, respectively:

(j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 129)

(k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 130) and

(l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 131), wherein Xaa may be any amino acid.

Using the assays described above, these polypeptides were shown to induce proliferation and IFN-γ production in PBMC preparations. Figs. 1A and B show the results of such assays using PBMC preparations from a first and a second donor, respectively.

DNA sequences that encode the antigens designated as (a), (c), (d) and (g) above were obtained by screening a *M. tuberculosis* genomic library using <sup>32</sup>P end

corresponding to antigen (a) above identified a clone having the sequence provided in SEQ ID No. 96. The polypeptide encoded by SEQ ID No. 96 is provided in SEQ ID No. 97. The screen performed using a probe corresponding to antigen (g) above identified a clone having the sequence provided in SEQ ID No. 52. The polypeptide encoded by SEQ ID No. 52 is provided in SEQ ID No. 53. The screen performed using a probe corresponding to antigen (d) above identified a clone having the sequence provided in SEQ ID No. 24, and the screen performed with a probe corresponding to antigen (c) identified a clone having the sequence provided in SEQ ID No. 25.

The above amino acid sequences were compared to known amino acid sequences in the gene bank using the DNA STAR system. The database searched contains some 173,000 proteins and is a combination of the Swiss, PIR databases along with translated protein sequences (Version 87). No significant homologies to the amino acid sequences for antigens (a)-(h) and (l) were detected.

The amino acid sequence for antigen (i) was found to be homologous to a sequence from *M. leprae*. The full length *M. leprae* sequence was amplified from genomic DNA using the sequence obtained from GENBANK. This sequence was then used to screen an *M. tuberculosis* library and a full length copy of the *M. tuberculosis* homologue was obtained (SEQ ID No. 94).

The amino acid sequence for antigen (j) was found to be homologous to a known *M. tuberculosis* protein translated from a DNA sequence. To the best of the inventors' knowledge, this protein has not been previously shown to possess T-cell stimulatory activity. The amino acid sequence for antigen (k) was found to be related to a sequence from *M. leprae*.

In the proliferation and IFN- $\gamma$  assays described above, using three PPD positive donors, the results for representative antigens provided above are presented in Table 1:

TABLE 1  
RESULTS OF PBMC PROLIFERATION AND IFN- $\gamma$  ASSAYS

Sequence	Proliferation	IFN- $\gamma$
(a)	+	-
(c)	+++	+++
(d)	++	++
(g)	+++	+++
(h)	+++	+++

- 5            In Table 1, responses that gave a stimulation index (SI) of between 2 and 4 (compared to cells cultured in medium alone) were scored as +, as SI of 4-8 or 2-4 at a concentration of 1  $\mu$ g or less was scored as ++ and an SI of greater than 8 was scored as +++.
- 10          The antigen of sequence (i) was found to have a high SI (+++) for one donor and lower SI (++ and +) for the two other donors in both proliferation and IFN- $\gamma$  assays.
- 10          These results indicate that these antigens are capable of inducing proliferation and/or interferon- $\gamma$  production.

EXAMPLE 2  
USE OF PATIENT SERA TO ISOLATE *M. TUBERCULOSIS* ANTIGENS

15

This example illustrates the isolation of antigens from *M. tuberculosis* lysate by screening with serum from *M. tuberculosis*-infected individuals.

Dessicated *M. tuberculosis* H37Ra (Difco Laboratories) was added to a 2% NP40 solution, and alternately homogenized and sonicated three times. The

20          resulting suspension was centrifuged at 13,000 rpm in microfuge tubes and the supernatant put through a 0.2 micron syringe filter. The filtrate was bound to Macro Prep DEAE Sepharose 6B (Pharmacia).

100  $\mu$ l of the filtrate was applied to a DEAE Sepharose 6B column. The column was treated with

DNase and RNase at 0.05 mg/ml for 30 min. at room temperature and then with  $\alpha$ -D-mannosidase, 0.5 U/mg at pH 4.5 for 3-4 hours at room temperature. After returning to pH 7.5, the material was fractionated via FPLC over a Bio Scale-Q-20 column (BioRad). Fractions were combined into nine pools, concentrated in a Centriprep 10 (Amicon, Beverley, MA) and screened by Western blot for serological activity using a serum pool from *M. tuberculosis*-infected patients which was not immunoreactive with other antigens of the present invention.

The most reactive fraction was run in SDS-PAGE and transferred to PVDF. A band at approximately 85 Kd was cut out yielding the sequence:

(m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 132), wherein Xaa may be any amino acid.

Comparison of this sequence with those in the gene bank as described above, revealed no significant homologies to known sequences.

### EXAMPLE 3

#### PREPARATION OF DNA SEQUENCES ENCODING *M. TUBERCULOSIS* ANTIGENS

This example illustrates the preparation of DNA sequences encoding *M. tuberculosis* antigens by screening a *M. tuberculosis* expression library with sera obtained from patients infected with *M. tuberculosis*, or with anti-sera raised against *M. tuberculosis* antigens.

#### A. PREPARATION OF *M. TUBERCULOSIS* SOLUBLE ANTIGENS USING RABBIT ANTI-SERA

Genomic DNA was isolated from the *M. tuberculosis* strain H37Ra. The DNA was randomly sheared and used to construct an expression library using the Lambda ZAP expression system (Stratagene, La Jolla, CA). Rabbit anti-sera

cultures. Specifically, the rabbit was first immunized subcutaneously with 200  $\mu$ g of protein antigen in a total volume of 2 ml containing 100  $\mu$ g muramyl dipeptide (Calbiochem, La Jolla, CA) and 1 ml of incomplete Freund's adjuvant. Four weeks later the rabbit was boosted subcutaneously with 100  $\mu$ g antigen in incomplete Freund's  
5 adjuvant. Finally, the rabbit was immunized intravenously four weeks later with 50  $\mu$ g protein antigen. The anti-sera were used to screen the expression library as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. Bacteriophage plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and  
10 the nucleotide sequences of the *M. tuberculosis* clones deduced.

Thirty two clones were purified. Of these, 25 represent sequences that have not been previously identified in *M. tuberculosis*. Proteins were induced by IPTG and purified by gel elution, as described in Skeiky et al., *J. Exp. Med.* 181:1527-1537, 1995. Representative partial sequences of DNA molecules identified in this screen are  
15 provided in SEQ ID Nos. 1-25. The corresponding predicted amino acid sequences are shown in SEQ ID Nos. 64-88.

On comparison of these sequences with known sequences in the gene bank using the databases described above, it was found that the clones referred to hereinafter as TbRA2A, TbRA16, TbRA18, and TbRA29 (SEQ ID Nos. 77, 69, 71, 76)  
20 show some homology to sequences previously identified in *Mycobacterium leprae* but not in *M. tuberculosis*. TbRA11, TbRA26, TbRA28 and TbDPEP (SEQ ID Nos. 66, 74, 75, 53) have been previously identified in *M. tuberculosis*. No significant homologies were found to TbRA1, TbRA3, TbRA4, TbRA9, TbRA10, TbRA13, TbRA17, TbRA19, TbRA29, TbRA32, TbRA36 and the overlapping clones TbRA35  
25 and TbRA12 (SEQ ID Nos. 64, 78, 82, 83, 65, 68, 76, 72, 76, 79, 81, 80, 67, respectively). The clone TbRa24 is overlapping with clone TbRa29.



B. USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING  
*M. TUBERCULOSIS* ANTIGENS

The genomic DNA library described above, and an additional H37Rv library, were screened using pools of sera obtained from patients with active tuberculosis. To prepare the H37Rv library, *M. tuberculosis* strain H37Rv genomic DNA was isolated, subjected to partial Sau3A digestion and used to construct an expression library using the Lambda Zap expression system (Stratagene, La Jolla, Ca). Three different pools of sera, each containing sera obtained from three individuals with active pulmonary or pleural disease, were used in the expression screening. The pools were designated TbL, TbM and TbH, referring to relative reactivity with H37Ra lysate (i.e., TbL = low reactivity, TbM = medium reactivity and TbH = high reactivity) in both ELISA and immunoblot format. A fourth pool of sera from seven patients with active pulmonary tuberculosis was also employed. All of the sera lacked increased reactivity with the recombinant 38 kD *M. tuberculosis* H37Ra phosphate-binding protein.

All pools were pre-adsorbed with *E. coli* lysate and used to screen the H37Ra and H37Rv expression libraries, as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. Bacteriophage plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the *M. tuberculosis* clones deduced.

Thirty two clones were purified. Of these, 31 represented sequences that had not been previously identified in human *M. tuberculosis*. Representative sequences of the DNA molecules identified are provided in SEQ ID NOS.: 26-51 and 100. Of these, TbH-8 and TbH-8-2 (SEQ. ID NO. 100) are non-contiguous DNA sequences from the same clone, and TbH-4 (SEQ. ID NO. 43) and TbH-4-FWD (SEQ. ID NO. 44) are non-contiguous sequences from the same clone. Amino acid sequences for the antigens hereinafter identified as Tb38-1, TbH-4, TbH-8, TbH-9, and TbH-12 are shown in SEQ ID NOS.: 89-93. Comparison of these sequences with known sequences

found to TbH-9. TbH-12 was found to be homologous to a 34 kD antigenic protein previously identified in *M. paratuberculosis* (Acc. No. S28515). Tb38-1 was found to be located 34 base pairs upstream of the open reading frame for the antigen ESAT-6 previously identified in *M. bovis* (Acc. No. U34848) and in *M. tuberculosis* (Sorensen et al., *Infect. Immun.* 63:1710-1717, 1995).

Probes derived from Tb38-1 and TbH-9, both isolated from an H37Ra library, were used to identify clones in an H37Rv library. Tb38-1 hybridized to Tb38-1F2, Tb38-1F3, Tb38-1F5 and Tb38-1F6 (SEQ. ID NOS. 107, 108, 111, 113, and 114) (SEQ ID NOS. 107 and 108 are non-contiguous sequences from clone Tb38-1F2.) Two open reading frames were deduced in Tb38-1F2; one corresponds to Tb37FL (SEQ. ID. NO. 109), the second, a partial sequence, may be the homologue of Tb38-1 and is called Tb38-IN (SEQ. ID NO. 110). The deduced amino acid sequence of Tb38-1F3 is presented in SEQ. ID. NO. 112. A TbH-9 probe identified three clones in the H37Rv library: TbH-9-FL (SEQ. ID NO. 101), which may be the homologue of TbH-9 (R37Ra), TbH-9-1 (SEQ. ID NO. 103), and TbH-9-4 (SEQ. ID NO. 105), all of which are highly related sequences to TbH-9. The deduced amino acid sequences for these three clones are presented in SEQ ID NOS. 102, 104 and 106.

20

#### EXAMPLE 4

##### PURIFICATION AND CHARACTERIZATION OF A POLYPEPTIDE FROM TUBERCULIN PURIFIED PROTEIN DERIVATIVE

An *M. tuberculosis* polypeptide was isolated from tuberculin purified protein derivative (PPD) as follows.

25

PPD was prepared as published with some modification (Seibert, F. et al., Tuberculin purified protein derivative. Preparation and analyses of a large quantity for standard. *The American Review of Tuberculosis* 44:9-25, 1941)

for 3 hours. Cultures were sterile filtered using a 0.22  $\mu$  filter and the liquid phase was concentrated 20 times using a 3 kD cut-off membrane. Proteins were precipitated once with 50% ammonium sulfate solution and eight times with 25% ammonium sulfate solution. The resulting proteins (PPD) were fractionated by reverse phase liquid chromatography (RP-HPLC) using a C18 column (7.8 x 300 mM; Waters, Milford, MA) in a Biocad HPLC system (Perseptive Biosystems, Framingham, MA). Fractions were eluted from the column with a linear gradient from 0-100% buffer (0.1% TFA in acetonitrile). The flow rate was 10 ml/minute and eluent was monitored at 214 nm and 280 nm.

10 Six fractions were collected, dried, suspended in PBS and tested individually in *M. tuberculosis*-infected guinea pigs for induction of delayed type hypersensitivity (DTH) reaction. One fraction was found to induce a strong DTH reaction and was subsequently fractionated further by RP-HPLC on a microbore Vydac C18 column (Cat. No. 218TP5115) in a Perkin Elmer/Applied Biosystems Division Model 172 HPLC. Fractions were eluted with a linear gradient from 5-100% buffer (0.05% TFA in acetonitrile) with a flow rate of 80  $\mu$ l/minute. Eluent was monitored at 215 nm. Eight fractions were collected and tested for induction of DTH in *M. tuberculosis*-infected guinea pigs. One fraction was found to induce strong DTH of about 16 mm induration. The other fractions did not induce detectable DTH. The positive fraction was submitted to SDS-PAGE gel electrophoresis and found to contain a single protein band of approximately 12 kD molecular weight.

This polypeptide, herein after referred to as DPPD, was sequenced from the amino terminal using a Perkin Elmer/Applied Biosystems Division Procise 492 protein sequencer as described above and found to have the N-terminal sequence shown in SEQ ID No.: 124. Comparison of this sequence with known sequences in the gene bank as described above revealed no known homologies. Four cyanogen bromide fragments of DPPD were isolated and found to have the sequences shown in SEQ ID Nos.: 125-128.

### EXAMPLE 5

#### SYNTHESIS OF SYNTHETIC POLYPEPTIDES

Polypeptides may be synthesized on a Millipore 9050 peptide  
5 synthesizer using Fmoc chemistry with HPTU (O-Benzotriazole-N,N,N',N'-  
tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be  
attached to the amino terminus of the peptide to provide a method of conjugation or  
labeling of the peptide. Cleavage of the peptides from the solid support may be carried  
out using the following cleavage mixture: trifluoroacetic  
10 acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the  
peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then  
be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior  
to purification by C18 reverse phase HPLC. A gradient of 0-60% acetonitrile  
(containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the  
15 peptides. Following lyophilization of the pure fractions, the peptides may be  
characterized using electrospray mass spectrometry and by amino acid analysis.

This procedure was used to synthesize a TbM-1 peptide that contains one  
and a half repeats of a TbM-1 sequence. The TbM-1 peptide has the sequence:  
GCGDRSGGNLDQIRLRDRSGGNL (SEQ ID No. 63).

20

### EXAMPLE 6

#### USE OF REPRESENTATIVE ANTIGENS FOR SERODIAGNOSIS OF TUBERCULOSIS

25 This Example illustrates the diagnostic properties of several  
representative antigens. Figures 1 and 2 present the reactivity of representative antigens  
with sera from *M. tuberculosis*-infected and uninfected individuals, as compared to the  
reactivity of bacterial lysate and the 38 kD antigen.

overnight at 4°C (or 2 hours at 37°C). The plate contents were then removed and the wells were blocked for 2 hours with 200 µL of PBS/1% BSA. After the blocking step, the wells were washed five times with PBS/0.1% Tween 20™. 50 µL sera, diluted 1:100 in PBS/0.1% Tween 20™/0.1% BSA, was then added to each well and incubated  
5 for 30 minutes at room temperature. The plates were then washed again five times with PBS/0.1% Tween 20™.

The enzyme conjugate (horseradish peroxidase - Protein A, Zymed, San Francisco, CA) was then diluted 1:10,000 in PBS/0.1% Tween 20™/0.1% BSA, and 50 µL of the diluted conjugate was added to each well and incubated for 30 minutes at  
10 room temperature. Following incubation, the wells were washed five times with PBS/0.1% Tween 20™. 100 µL of tetramethylbenzidine peroxidase (TMB) substrate (Kirkegaard and Perry Laboratories, Gaithersburg, MD) was added, undiluted, and incubated for about 15 minutes. The reaction was stopped with the addition of 100 µL of 1 N H<sub>2</sub>SO<sub>4</sub> to each well, and the plates were read at 450 nm.

15 Figure 2 shows the ELISA reactivity of two recombinant antigens isolated using method A in Example 3 (TbRa3 and TbRa9) with sera from *M. tuberculosis* positive and negative patients. The reactivity of these antigens is compared to that of bacterial lysate isolated from *M. tuberculosis* strain H37Ra (Difco, Detroit, MI). In both cases, the recombinant antigens differentiated positive from  
20 negative sera. Based on cut-off values obtained from receiver-operator curves, TbRa3 detected 56 out of 87 positive sera, and TbRa9 detected 111 out of 165 positive sera.

Figure 3 illustrates the ELISA reactivity of representative antigens isolated using method B of Example 3. The reactivity of the recombinant antigens TbH4, TbH12, Tb38-1 and the peptide TbM-1 (as described in Example 4) is compared  
25 to that of the 38 kD antigen described by Andersen and Hansen, *Infect. Immun.* 57:2481-2488, 1989. Again, all of the polypeptides tested differentiated positive from negative sera. Based on cut-off values obtained from receiver-operator curves, TbH4 detected 67 out of 126 positive sera. TbH12 detected 59 out of 125 positive sera.

The reactivity of four antigens (TbRa3, TbRa9, TbH4 and TbH12) with sera from a group of *M. tuberculosis* infected patients with differing reactivity in the acid fast stain of sputum (Smithwick and David, *Tubercle* 52:226, 1971) was also examined, and compared to the reactivity of *M. tuberculosis* lysate and the 38 kD antigen. The results are presented in Table 2, below:

**TABLE 2**  
**REACTIVITY OF ANTIGENS WITH SERA FROM *M. TUBERCULOSIS* PATIENTS**

Patient	Acid Fast Sputum	ELISA Values					
		Lysate	38kD	TbRa9	TbH12	TbH4	TbRa3
Tb01B93I-2	++++	1.853	0.634	0.998	1.022	1.030	1.314
Tb01B93I-19	++++	2.657	2.322	0.608	0.837	1.857	2.335
Tb01B93I-8	+++	2.703	0.527	0.492	0.281	0.501	2.002
Tb01B93I-10	+++	1.665	1.301	0.685	0.216	0.448	0.458
Tb01B93I-11	+++	2.817	0.697	0.509	0.301	0.173	2.608
Tb01B93I-15	+++	1.28	0.283	0.808	0.218	1.537	0.811
Tb01B93I-16	+++	2.908	>3	0.899	0.441	0.593	1.080
Tb01B93I-25	+++	0.395	0.131	0.335	0.211	0.107	0.948
Tb01B93I-87	+++	2.653	2.432	2.282	0.977	1.221	0.857
Tb01B93I-89	+++	1.912	2.370	2.436	0.876	0.520	0.952
Tb01B94I-108	+++	1.639	0.341	0.797	0.368	0.654	0.798
Tb01B94I-201	+++	1.721	0.419	0.661	0.137	0.064	0.692
Tb01B93I-88	++	1.939	1.269	2.519	1.381	0.214	0.530

Patient	Acid Fast Sputum	ELISA Values					
		Lysate	38kD	TbRa9	TbH12	TbH4	TbRa3
Tb01B94I-210	++	2.777	>3	0.393	0.367	1.004	1.315
Tb01B94I-224	++	2.913	0.476	0.251	1.297	1.990	0.256
Tb01B93I-9	+	2.649	0.278	0.210	0.140	0.181	1.586
Tb01B93I-14	+	>3	1.538	0.282	0.291	0.549	2.880
Tb01B93I-21	+	2.645	0.739	2.499	0.783	0.536	1.770
Tb01B93I-22	+	0.714	0.451	2.082	0.285	0.269	1.159
Tb01B93I-31	+	0.956	0.490	1.019	0.812	0.176	1.293
Tb01B93I-32	-	2.261	0.786	0.668	0.273	0.535	0.405
Tb01B93I-52	-	0.658	0.114	0.434	0.330	0.273	1.140
Tb01B93I-99	-	2.118	0.584	1.62	0.119	0.977	0.729
Tb01B94I-130	-	1.349	0.224	0.86	0.282	0.383	2.146
Tb01B94I-131	-	0.685	0.324	1.173	0.059	0.118	1.431
AT4-0070	Normal	0.072	0.043	0.092	0.071	0.040	0.039
AT4-0105	Normal	0.397	0.121	0.118	0.103	0.078	0.390
3/15/94-1	Normal	0.227	0.064	0.098	0.026	0.001	0.228
4/15/93-2	Normal	0.114	0.240	0.071	0.034	0.041	0.264
5/26/94-4	Normal	0.089	0.259	0.096	0.046	0.008	0.053
5/26/94-3	Normal	0.139	0.093	0.085	0.019	0.067	0.01

Based on cut-off values obtained from receiver-operator curves, TbRa3 detected 23 out of 27 positive sera. TbRa9 detected 22 out of 27. TbH12 detected 21 out of 27. TbH4 detected 20 out of 27. TbRa3 and TbRa9 complement each other in the serological detection of *M. tuberculosis* infection.

In addition, several of the recombinant antigens detected positive sera that were not detected using the 38 kD antigen, indicating that these antigens may be complementary to the 38 kD antigen.

The reactivity of the recombinant antigen TbRa11 with sera from  
5 *M. tuberculosis* patients shown to be negative for the 38 kD antigen, as well as with sera from PPD positive and normal donors, was determined by ELISA as described above. The results are shown in Figure 4 which indicates that TbRa11, while being negative with sera from PPD positive and normal donors, detected sera that were negative with the 38 kD antigen. Of the thirteen 38 kD negative sera tested, nine were positive with  
10 TbRa11, indicating that this antigen may be reacting with a sub-group of 38 kD antigen negative sera. In contrast, in a group of 38 kD positive sera where TbRa11 was reactive, the mean OD 450 for TbRa11 was lower than that for the 38 kD antigen. The data indicate an inverse relationship between the presence of TbRa11 activity and 38 kD positivity.

15 The antigen TbRa2A was tested in an indirect ELISA using initially 50 µl of serum at 1:100 dilution for 30 minutes at room temperature followed by washing in PBS Tween and incubating for 30 minutes with biotinylated Protein A (Zymed, San Francisco, CA) at a 1:10,000 dilution. Following washing, 50 µl of streptavidin-horseradish peroxidase (Zymed) at 1:10,000 dilution was added and the  
20 mixture incubated for 30 minutes. After washing, the assay was developed with TMB substrate as described above. The reactivity of TbRa2A with sera from *M. tuberculosis* patients and normal donors is shown in Table 3. The mean value for reactivity of TbRa2A with sera from *M. tuberculosis* patients was 0.444 with a standard deviation of 0.309. The mean for reactivity with sera from normal donors was 0.109 with a standard  
25 deviation of 0.029. Testing of 38 kD negative sera (Figure 5) also indicated that the TbRa2A antigen was capable of detecting sera in this category.



TABLE 3  
 REACTIVITY OF TbRa2A WITH SERA FROM *M. TUBERCULOSIS* PATIENTS AND FROM  
 NORMAL DONORS

Serum ID	Status	OD 450
Tb85	TB	0.680
Tb86	TB	0.450
Tb87	TB	0.263
Tb88	TB	0.275
Tb89	TB	0.403
Tb91	TB	0.393
Tb92	TB	0.401
Tb93	TB	0.232
Tb94	TB	0.333
Tb95	TB	0.435
Tb96	TB	0.284
Tb97	TB	0.320
Tb99	TB	0.328
Tb100	TB	0.817
Tb101	TB	0.607
Tb102	TB	0.191
Tb103	TB	0.228
Tb107	TB	0.324
Tb109	TB	1.572
Tb112	TB	0.338
DL4-0176	Normal	0.036
AT4-0043	Normal	0.126
AT4-0044	Normal	0.130
AT4-0052	Normal	0.135
AT4-0053	Normal	0.133
AT4-0062	Normal	0.128
AT4-0070	Normal	0.088
AT4-0091	Normal	0.108
AT4-0100	Normal	0.106
AT4-0105	Normal	0.108
AT4-0109	Normal	0.105

*M. tuberculosis* positive sera that were all reactive with the 38 kD antigen and with four donor sera. All four positive sera were reactive with antigen (g).

From the foregoing, it will be appreciated that, although specific  
5 embodiments of the invention have been described herein for the purpose of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

- (i) APPLICANTS: Corixa Corporation
- (ii) TITLE OF INVENTION: COMPOUNDS AND METHODS FOR DIAGNOSIS OF  
TUBERCULOSIS
- (iii) NUMBER OF SEQUENCES: 132
- (iv) CORRESPONDENCE ADDRESS:
  - (A) ADDRESSEE: SEED and BERRY LLP
  - (B) STREET: 6300 Columbia Center, 701 Fifth Avenue
  - (C) CITY: Seattle
  - (D) STATE: Washington
  - (E) COUNTRY: USA
  - (F) ZIP: 98104-7092
- (v) COMPUTER READABLE FORM:
  - (A) MEDIUM TYPE: Floppy disk
  - (B) COMPUTER: IBM PC compatible
  - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
  - (D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- (vi) CURRENT APPLICATION DATA:
  - (A) APPLICATION NUMBER:
  - (B) FILING DATE: 27-AUG-1996
  - (C) CLASSIFICATION:

## (viii) ATTORNEY/AGENT INFORMATION:

- (A) NAME: Maki, David J.
- (B) REGISTRATION NUMBER: 31.392
- (C) REFERENCE/DOCKET NUMBER: 210121.417PC

## (ix) TELECOMMUNICATION INFORMATION:

- (A) TELEPHONE: (206) 622-4900
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## (2) INFORMATION FOR SEQ ID NO:1:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 766 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CGAGGCACCG GTAGTTTGAA CCAAACGCAC AATCGACGGG CAAACGAACG GAAGAACACA	60
ACCATGAAGA TGGTGAAATC GATCGCCGCA GGTCTGACCG CCGCGGCTGC AATCGGCGCC	120
GCTGCGGCCG GTGTGACTTC GATCATGGCT GCGGCCCCGG TCGTATACCA GATGCAGCCG	180
GTCGTCTTCG GCGCGCCACT GCGGTTGGAC CCGGCATCCG CCCCTGACGT CCGACCGCC	240
GCCCAGTTGA CCAGCCTGCT CAACAGCCTC GCGGATCCCA ACGTGTCGTT TGCGAACAAG	300
GGCAGTCTGG TCGAGGGCGG CATCGGGGGC ACCGAGGCGC GCATCGCCGA CCACAAGCTG	360
AAGAAGGCCG CCGAGCACGG GGATCTGCCG CTGTCGTTCA GCGTGACGAA CATCCAGCCG	420

GCGGCCGCCG GTTCGGCCAC CGCCGACGTT TCCGTCTCGG GTCCGAAGCT CTCGTGCGCCG 480  
GTCACGCAGA ACGTCACGTT CGTGAATCAA GGC GGCTGGA TGCTGTCACG CGCATCGGCG 540  
ATGGAGTTGC TGCAGGCCGC AGGGNAACTG ATTEGGCGGC CGGNTTCAGC CCGCTGTTCA 600  
GCTACGCCGC CCGCCTGGTG ACGCGTCCAT GTCGAACACT CGCGCGTGTA GCACGGTGCG 660  
GTNTGCGCAG GGNCGCACGC ACCGCCCGGT GCAAGCCGTC CTCGAGATAG GTGGTGNCTC 720  
GNCACCAGNG ANCACCCCN NNTCGNCNNT TCTCGNTGNT GNATGA 766

## (2) INFORMATION FOR SEQ ID NO:2:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 752 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

ATGCATCACC ATCACCATCA CGATGAAGTC ACGGTAGAGA CGACCTCCGT CTTCCGCGCA 60  
GACTTCCTCA GCGAGCTGGA CGCTCCTGCG CAAGCGGGTA CGGAGAGCGC GGTCTCCGGG 120  
GTGGAAGGGC TCCGCCGGG CTGGCGTTG CTGGTAGTCA AACGAGGCC CAACGCCGGG 180  
TCCCGGTTCC TACTCGACCA AGCCATCAG TCGGCTGGTC GGCATCCCGA CAGCGACATA 240  
TTTCTCGACG ACGTGACCGT GAGCCGTCGC CATGCTGAAT TCCGGTTGGA AAACAACGAA 300

TTCAATCTCG

ACCGGACCCA AGCAAGGCGA GGATGACGGG AGTACCGGGG GCCCGTGAGC GCACCCGATA	480
GCCCCGCGCT GGCCGGGATG TCGATCGGGG CGGTCTCCG ACCTGCTACG ACCGGATTTT	540
CCCTGATGTC CACCATCTCC AAGATTCGAT TCTTGGGAGG CTTGAGGGTC NGGGTGACCC	600
CCCCGCGGGC CTCATTGNGG GGTNTCGGCN GGTTTCACCC CNTACCNACT GCCNCCCGN	660
TTGCNAATTC NTTCTTCNCT GGCNNAAAG GGACNNTTAN CTTGCCGCTN GAAANGGTNA	720
TCCNGGGCCC NTCCTNGAAN CCCNTCCCC CT	752

## (2) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 813 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CATATGCATC ACCATCACCA TCACACTTCT AACGCCCCAG CGGTCGGGG GCGTCGAGCA	60
CCACGCGACA CCGGGCCCGA TCGATCTGCT AGCTTGAGTC TGGTCAGGCA TCGTCGTCAG	120
CAGCGCGATG CCCTATGTTT GTCGTCGACT CAGATATCGC GGCAATCCAA TCTCCCGCCT	180
GCGGCCGGCG GTGCTGCAAA CTACTCCCGG AGGAATTTG ACGTGCGCAT CAAGATCTTC	240
ATGCTGGTCA CGGCTGTCGT TTTGCTCTGT TGTTCGGGTG TGGGACGGG GCGGCGGAA	300

GACCCGGCCT ACAACATCAA CATCAGCCTG CCCAGTTACT ACCCCGACCA GAAGTCGCTG 420  
GAAAATTACA TCGCCCAGAC GCGCGACAAG TTCCTCAGCG CGGCCACATC GTCCACTCCA 480  
CGCGAAGCCC CCTACGAATT GAATATCACC TCGGCCACAT ACCAGTCCGC GATACCGCCG 540  
CGTGGTACGC AGGCCGTGGT GCTCAMGGTC TACCACAACG CCGGCGGCAC GCACCCAACG 600  
ACCACGTACA AGGCCTTCGA TTGGGACCAG GCCTATCGCA AGCCAATCAC CTATGACACG 660  
CTGTGGCAGG CTGACACCGA TCCGCTGCCA GTCGTCTTCC CCATTGTTGC AAGGTGAACT 720  
GAGCAACGCA GACCGGGACA ACWGGTATCG ATAGCCGCCN AATGCCGGCT TGAACCCNG 780  
TGAAATTATC ACAACTTCGC AGTCACNAAA NAA 813

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 447 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:4:

CGGTATGAAC ACGGCCGCGT CCGATAACTT CCAGCTGTCC CAGGGTGGGC AGGGATTTCG 60  
CATTCCGATC GGGCAGGCGA TGGCGATCGC GGGCCAGATC CGATCGGGTG GGGGGTCACC 120  
CACCGTTCAT ATCGGGCCTA CCGCCTTCCT CGGCTTGGGT GTTGTGACACA ACAACGGCAA 180

CGCGCTTAAC GGGCATCATC CCGGTGACGT CATCTCGGTG AACTGGCAAA CCAAGTCGGG 360  
CGGCACGCGT ACAGGGAACG TGACATTGGC CGAGGGACCC CCGGCCTGAT TTCGTCGYGG 420  
ATACCACCCG CCGGCCGGCC AATTGGA 447

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 604 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GTCCCACTGC GGTCCCGAG TATGTCGCC AGCAAATGTC TGGCAGCCGC CCAACGGAAT 60  
CCGGTGATCC GACGTCGAG GTTGTCGAAC CCGCCGCCGC GGAAGTATCG GTCCATGCCT 120  
AGCCCGGCGA CGGCGAGCGC CGGAATGGCG CGAGTGAGGA GGCGGGCAAT TTGGCGGGGC 180  
CCGGCGACGG NGAGCGCCGG AATGGCGCGA GTGAGGAGGT GGNCAGTCAT GCCCAGNGTG 240  
ATCCAATCAA CCTGNATTCG GNCTGNNGGN CCATTTGACA ATCGAGGTAG TGAGCGCAAA 300  
TGAATGATGG AAAACGGGNG GNGACGTCCG NTGTTCTGGT GGTGNTAGGT GNCTGNCTGG 360  
NGTNGNGGNT ATCAGGATGT TCTTCGNCGA AANCTGATGN CGAGGAACAG GGTGTNCCCG 420  
NNANCCNAN GNGTCCNAN CCGNNNTCC TCGNCGANAT CANANAGNG NTGATGNGA



NNNTNTTNC ANNNNNNTG NNGNNGNCCN NNNCAANCNN NTNNNGNAA NNGGNTTNTT 600

NAAT 604

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 633 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TTGCANGTCG AACCACCTCA CTAAAGGGAA CAAAAGCTNG AGCTCCACCG CGGTGGCGGC 60  
CGCTCTAGAA CTAGTGKATM YYYCKGGCTG CAGSAATYCG GYACGAGCAT TAGGACAGTC 120  
TAACGGTCCT GTTACGGTGA TCGAATGACC GACGACATCC TGCTGATCGA CACCGACGAA 180  
CGGGTGCGAA CCCTCACCCT CAACCGGCCG CAGTCCCGYA ACGCGCTCTC GGCGGCGCTA 240  
CGGGATCGGT TTTTCGCGGY GTTGGYCGAC GCCGAGGYCG ACGACGACAT CGACGTCGTC 300  
ATCCTCACCG GYGCCGATCC GGTGTTCTGC GCCGACTGG ACCTCAAGGT AGCTGGCCGG 360  
GCAGACCGCG CTGCCGGACA TCTACCGCG GTGGCGGCC ATGACCAAGC CGGTGATCGG 420  
CGCGATCAAC GGCGCCGCGG TCACCGGCGG GCTCGAACTG GCGCTGTACT GCGACATCCT 480  
GATCGCCTCC GAGCACGCC GCTTCGNCGA CACCCACGCC CGGGTGGGGC TGCTGCCAC 540

## (2) INFORMATION FOR SEQ ID NO:7:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1362 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CGACGACGAC GGC GCCGAG AGCGGGCGCG AACGGCGATC GACGCGGCC TGGCCAGAGT	60
CGGCACCACC CAGGAGGGAG TCGAATCATG AAATTGTCA ACCATATTGA GCCCGTCGCG	120
CCCCGCCGAG CCGGCGGCGC GGTGCGCGAG GTCTATGCCG AGGCCCGCCG CGAGTTCGCG	180
CGGCTGCCCC AGCCGCTCGC CATGCTGTCC CCGGACGAGG GACTGCTCAC CGCCGGCTGG	240
GCGACGTTGC GCGAGACACT GCTGGTGGGC CAGGTGCCGC GTGGCCGCAA GGAAGCCGTC	300
GCCGCCGCCG TCGCGGCCAG CCTGCGCTGC CCCTGGTGCG TCGACGCACA CACCACCATG	360
CTGTACGCGG CAGGCCAAAC CGACACCGCC GCGGCGATCT TGGCCGGCAC AGCACCTGCC	420
GCCGGTGACC CGAACGCGCC GTATGTGGCG TGGGCGGCAG GAACCGGGAC ACCGSCGGGA	480
CCGCCGGCAC CGTTCGGCCC GGATGTCGCC GCCGAATACC TGGGCACCGC GGTGCAATTC	540
CAC TTCATCG CACGCCTGGT CCTGGTGCTG CTGGACGAAA CCTTCCTGCC GGGGGGCCCC	600
CGCGCCCAAC AGCTCATGCG CCGCGCGGCT GGACTGGTGT TGGCCGCAA GGTGCGGCG	660

GCATGGGCAA CACCGTCCGA GCCCATAGCA ACCGCGTTCG CCGCGCTCAG CCACCACCTG 780  
GACACCGCGC CGCACCTGCC GCCACCGACT CGTCAGGTGG TCAGGCGGGT CGTGGGGTCG 840  
TGGCACGGCG AGCCAATGCC GATGAGCAGT CGCTGGACGA ACGAGCACAC CGCCGAGCTG 900  
CCCGCCGACC TGCACGCGCC CACCCGTCTT GCCCTGCTGA CCGGCCTGGC CCCGCATCAG 960  
GTGACCGACG ACGACGTCGC CGCGGCCCGA TCCCTGCTCG ACACCGATGC GGCCTGTT 1020  
GGCGCCCTGG CCTGGGCCGC CTTACCGCC GCGCGGCGCA TCGGCACCTG GATCGGCGCC 1080  
GCCGCCGAGG GCCAGGTGTC GCGGCAAAAC CCGACTGGGT GAGTGTGCGC GCCCTGTCGG 1140  
TAGGGTGTC TCGCTGGCCC GAGGGATCTC GCGGCGGCGA ACGGAGGTGG CGACACAGGT 1200  
GGAAGCTGCG CCCACTGGCT TGCGCCCCAA CGCGTCGTG GCGTTCGGT TGGCCGCACT 1260  
GGCCGATCAG GTCGGCGCCG GCCCTTGCC GAAGGTCCAG CTCAACGTGC CGTCACCGAA 1320  
GGACCGGACG GTCACCGGGG GTCACCCTGC GCGCCAAGG AA 1362

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1458 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION. SEQ ID NO:8:

TGGATGACGT GGCCCGTGTT TACATCATCT ACCGGCAGCG GCGCGCCGAG CTGCGGACGG 180  
CTAAGGCCTT GCTCGGCGTG CGGGACGAGT TAAAGCTGAG CTTGGCGGCC GTGACGGTAC 240  
TGCGCGAGCG CTATCTGCTG CACGACGAGC AGGGCCGGCC GGCCGAGTCG ACCGGCGAGC 300  
TGATGGACCG ATCGGCGCGC TGTGTCGCGG CGGCCGAGGA CCAGTATGAG CCGGGCTCGT 360  
CGAGGCGGTG GGCCGAGCGG TTCGCCACGC TATTACGCAA CCTGGAATTC CTGCCGAATT 420  
CGCCACGTT GATGAACTCT GGCACCGACC TGGGACTGCT CGCCGGCTGT TTTGTTCTGC 480  
CGATTGAGGA TTCGCTGCAA TCGATCTTTG CGACGCTGGG ACAGGCCGCC GAGCTGCAGC 540  
GGGCTGGAGG CGGCACCGGA TATGCGTTCA GCCACCTGCG ACCCGCCGGG GATCGGGTGG 600  
CCTCCACGGG CGGCACGGCC AGCGGACCGG TGTCGTTTCT ACGGCTGTAT GACAGTGCCG 660  
CGGGTGTGGT CTCCATGGGC GGTGCGCCGC GTGGCGCCTG TATGGCTGTG CTTGATGTGT 720  
CGCACCCGGA TATCTGTGAT TTCGTCACCG CCAAGGCCGA ATCCCCAGC GAGCTCCCGC 780  
ATTTCAACCT ATCGGTTGGT GTGACCGACG CGTTCCTGCG GGCCGTCGAA CGCAACGGCC 840  
TACACCGGCT GGTCAATCCG CGAACCGGCA AGATCGTCGC GCGGATGCCC GCCGCCGAGC 900  
TGTTGACGC CATCTGCAA GCGCGCACG CCGGTGGCGA TCCCGGGCTG GTGTTTCTCG 960  
ACACGATCAA TAGGGCAAAC CCGGTGCCGG GGAGAGGCCG CATCGAGGCG ACCAACCCGT 1020  
GCGGGGAGGT CCCACTGCTG CCTTACGAGT CATGTAATCT CGGCTCGATC AACCTCGCCC 1080

CGGCCCGCGC CACCCGCAAG ATCGGGCTGG GAGTCATGGG TTTGGCGGAA CTGCTTGCCG 1260  
CACTGGGTAT TCCGTACGAC AGTGAAGAAG CCGTGCGGTT AGCCACCCGG CTCATGCGTC 1320  
GCATACAGCA GGCGGCGCAC ACGGCATCGC GGAGGCTGGC CGAAGAGCGG GGCGCATTCC 1380  
CGGCGTTCAC CGATAGCCGG TTCGCGCGGT CGGGCCCGAG GCGCAACGCA CAGGTCACCT 1440  
CCGTGCTCC CACGGGCA 1458

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 862 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

ACGGTGTAAT CGTGCTGGAT CTGGAACCGC GTGGCCCGCT ACCTACCGAG ATCTACTGGC 60  
GGCGCAGGGG GCTGGCCCTG GGCATCGCGG TCGTCGTAGT CGGGATCGCG GTGGCCATCG 120  
TCATCGCCTT CGTCGACAGC AGCGCCGGTG CCAAACCGGT CAGCGCCGAC AAGCCGGCCT 180  
CCGCCAGAG CCATCCGGGC TCGCCGGCAC CCCAAGCACC CCAGCCGGCC GGGCAAACCG 240  
AAGGTAACGC CGCCGCGGCC CCGCCGAGG GCCAAAACCC CGAGACACCC ACGCCACCG 300  
CCGCGGTGCA GCGCGCGCGG GTGCTCAAGG AAGCGGACCA TCGCCCGAT TCGACCTCC

TGGTGGTCAC CAACATCGGC CTGGTGCCT GTAAACGCGA CGTTGGGGCC GCGGTGTTGG 480  
CCGCTACGT TTA CTCTGCTG GACAACAAGC GGTGTGGTC CAACCTGGAC TGC GCGCCCT 540  
CGAATGAGAC GCTGCTCAAG ACGTTTCCC CCGGTGAGCA GGTAACGACC GCGGTGACCT 600  
GGACCGGGAT GGGATCGGCG CCGCGCTGCC CATTGCCGCG GCCGGCGATC GGGCCGGGCA 660  
CCTACAATCT CGTGGTACAA CTGGGCAATC TGCCTCGCT GCCGGTTCCG TTCATCCTGA 720  
ATCAGCCGCC GCCGCCGCC GGGCCGGTAC CCGCTCCGGG TCCAGCGCAG GCGCCTCCGC 780  
CGGAGTCTCC CCGCAAGGC GGATAATTAT TGATCGCTGA TGGTCGATTG CGCCAGCTGT 840  
GACAACCCCT CGCCTCGTGC CG 862

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 622 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TTGATCAGCA CCGGCAAGGC GTCACATGCC TCCCTGGGTG TGCAGGTGAC CAATGACAAA 60  
GACACCCCGG GCGCCAAGAT CGTCGAAGTA GTGGCCGGTG GTGCTGCCGC GAACGCTGGA 120  
GTGCCGAAGG GCGTCGTTGT CACCAAGGTC GACGACCGCC CGATCAACAG CGCGGACGCG 180

TCGCCGCGCA GTGTTCAAAG CTCGGATATA CGGTGGCACC CATGGAACAG CGTGCGGAGT 360  
 TGGTGGTTGG CCGGGCACTT GTCGTCGTCG TTGACGATCG CACGGCGCAC GGCATGAAG 420  
 ACCACAGCGG GCCGCTTGTC ACCGAGCTGC TCACCGAGGC CGGGTTTGTT GTCGACGGCG 480  
 TGGTGGCGGT GTCGGCCGAC GAGGTCGAGA TCCGAAATGC GCTGAACACA GCGGTGATCG 540  
 GCGGGGTGGA CCTGGTGGTG TCGGTGGCG CGACCGGNGT GACGNTCGC GATGTCACCC 600  
 CGGAAGCCAC CCGNGACATT CT 622

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1200 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GGCGCAGCGG TAAGCCTGTT GGCCGCCGGC AACTGGTGT TGACAGCATG CGGCGGTGGC 60  
 ACCAACAGCT CGTCGTCAGG CGCAGGCGGA ACGTCTGGGT CGGTGCACTG CGGCGGCAAG 120  
 AAGGAGCTCC ACTCCAGCGG CTCGACCGCA CAAGAAAATG CCATGGAGCA GTTCGTCTAT 180  
 GCCTACGTGC GATCGTGCCC GGGCTACAG TTGGACTACA ACGCCAACGG GTCCGGTGCC 240  
 GGGGTGACCC AGTTTCTCAA CAACGAACC GATTTGCGCG GTCGGATGT CCGGTTCAAT 300

CCGACGGTGT TCGGCCCGAT CGCGATCACC TACAATATCA AGGGCGTGAG CACGCTGAAT	420	-
CTTGACGGAC CCACTACCGC CAAGATTTTC AACGGCACCA TCACCGTGTG GAATGATCCA	480	-
CAGATCCAAG CCCTCAACTC CGGCACCGAC CTGCCGCCAA CACCGATTAG CGTTATCTTC	540	
CGCAGCGACA AGTCCGGTAC GTCGGACAAC TTCCAGAAAT ACCTCGACGG TGTATCCAAC	600	
GGGGCGTGGG GCAAAGGGC CAGCGAAACG TTCAGCGGGG GCGTCGGCGT CGGCGCCAGC	660	
GGGAACAACG GAACGTCGGC CCTACTGCAG ACGACCGAAG GGTGATCAC CTACAACGAG	720	
TGGTCGTTTG CGGTGGGTAA GCAGTTGAAC ATGGCCAGA TCATCACGTC GCGGGGTCCG	780	
GATCCAGTGG CGATCACCAC CGAGTCGGTC GGTAAGACAA TCGCCGGGGC CAAGATCATG	840	
GGACAAGGCA ACGACCTGGT ATTGGACAG TCGTCGTTCT ACAGACCCAC CCAGCCTGGC	900	
TCTTACCCGA TCGTGCTGGC GACCTATGAG ATCGTCTGCT CGAAATACCC GGATGCGACG	960	
ACCGGTACTG CGGTAAGGGC GTTTATGCAA GCCGCGATTG GTCCAGGCCA AGAAGGCCTG	1020	
GACCAATACG GCTCCATTCC GTTGCCCAA TCGTTCCAAG CAAAATTGGC GGCCGCGGTG	1080	
AATGCTATTT CTTGACCTAG TGAAGGGAAT TCGACGGTGA GCGATGCCGT TCCGAGGTA	1140	
GGGTCGCAAT TTGGGCCGTA TCAGCTATTG CGGCTGCTGG GCCGAGGCGG GATGGGCGAG	1200	

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1155 base pairs



## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GCAAGCAGCT GCAGGTCGTG CTGTTGACG AACTGGGCAT GCCGAAGACC AAACGCACCA	60
AGACCGGCTA CACCACGGAT GCCGACGCGC TGCAGTCGTT GTTCGACAAG ACCGGGCATC	120
CGTTTCTGCA ACATCTGCTC GCCCACC GCG ACGTCACCCG GCTCAAGGTC ACCGTCGACG	180
GGTTGCTCCA AGCGGTGGCC GCCGACGGCC GCATCCACAC CACGTTCAAC CAGACGATCG	240
CCGCGACCGG CCGGCTCTCC TCGACCGAAC CCAACCTGCA GAACATCCCG ATCCGCACCG	300
ACGCGGGCCG GCGGATCCGG GACGCGTTG TGGTCGGGGA CGGTTACGCC GAGTTGATGA	360
CGGCCGACTA CAGCCAGATC GAGATGCGGA TCATGGGGCA CCTGTCCGGG GACGAGGGCC	420
TCATCGAGGC GTTCAACACC GGGGAGGACC TGTATTCGTT CGTCGCGTCC CGGGTGTTG	480
GTGTGCCCAT CGACGAGGTC ACCGGCGAGT TCGGCGCCG GGTCAAGGCG ATGTCCTACG	540
GGCTGGTTTA CGGGTTGAGC GCCTACGGCC TGTCGCAGCA GTTGAAAATC TCCACCGAGG	600
AAGCCAACGA GCAGATGGAC GCGTATTTG CCCGATTGCG CGGGGTGCGC GACTACCTGC	660
GGCCCGTAGT CGAGCGGGCC CGCAAGGACG GCTACACCTC GACGGTGCTG GGCCGTCGCC	720
GCTACCTGCC CGAGCTGGAC AGCAGCAACC GTCAAGTGCG GGAGGCCGCC GAGCGGGCGG	780
CGCTGAACGC GCCGATCCAG GGCAGCGCGG CCGACATCAT CAAGGTGGCC ATGATCCAGG	840
TCGACAAGGC GCTCAACGAG GCACAGCTG CGTCGGCAT GGTGCTGAG GTCCAGGACG	900

AGATGGGCGG CGCTTACCCG CTCGACGTCC CGCTGGAGGT GTCGGTGGGC TACGGCCGCA 1020  
 GCTGGGACGC GCGGGCGCAC TGAGTGCCGA GCGTGATCT GGGGCGGGAA TTCGGCGATT 1080  
 TTTCCGCCCT GAGTTCACGC TCGGCGCAAT CGGGACCGAG TTTGTCCAGC GTGTACCCGT 1140  
 CGAGTAGCCT CGTCA 1155

## (2) INFORMATION FOR SEQ ID NO:13:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1771 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAGCGCCGTC TGGTGTTTGA ACGGTTTTAC CGGTCGGCAT CGGCACGGGC GTTGCCGGGT 60  
 TCGGGCCTCG GGTGGCGAT CGTCAAACAG GTGGTGCTCA ACCACGGCGG ATTGCTGCGC 120  
 ATCGAAGACA CCGACCCAGG CGGCCAGCCC CCTGGAACGT CGATTACGT GCTGCTCCCC 180  
 GGCCGTCGGA TGCCGATTCC GCAGCTTCCC GGTGCGACGG CTGGCGCTCG GAGCACGGAC 240  
 ATCGAGAACT CTCGGGGTTC GGCGAACGTT ATCTCAGTGG AATCTCAGTC CACGCGCGCA 300  
 ACCTAGTTGT GCAGTTACTG TTGAAAGCCA CACCCATGCC AGTCCACGCA TGGCCAAGTT 360  
 GGCCCGAGTA GTGGGCCTAG TACAGGAAGA GCAACCTAGC GACATGACGA ATCACCACG 420

CCGTCAACCC TACGAGGCGT TGGGTGGTAC CCGGCCGGGT CTGATACCTG GCGTGATTCC 600  
GACCATGACG CCCCTCCTG GGATGGTTCG CCAACGCCCT CGTGCAGGCA TGTGGCCAT 660  
CGGCGCGGTG ACGATAGCGG TGGTGCCGC CGGCATCGGC GCGCGGCCG CATCCCTGGT 720  
CGGGTTCAAC CGGGCACCCG CCGGCCCCAG CGGCGGCCCA GTGGCTGCCA GCGCGGCGCC 780  
AAGCATCCCC GCAGCAAACA TGCCGCCGGG GTGGGTGAA CAGGTGGCGG CCAAGGTGGT 840  
GCCCAGTGTC GTCATGTTGG AAACCGATCT GGGCCGCCAG TCGGAGGAGG GCTCCGGCAT 900  
CATTCTGTCT GCCGAGGGGC TGATCTTGAC CAACAACCAC GTGATCGCGG CGGCCGCCAA 960  
GCCTCCCCTG GGCAGTCCGC CGCCGAAAAC GACGGTAACC TTCTCTGACG GCGGGACCGC 1020  
ACCTTCACG GTGGTGGGGG CTGACCCAC CAGTGATATC GCCGTCGTCC GTGTTCAGGG 1080  
CGTCTCCGGG CTCACCCGA TCTCCCTGGG TTCCTCCTCG GACCTGAGGG TCGGTCAGCC 1140  
GGTGCTGGCG ATCGGGTCGC CGCTCGGTTT GGAGGGCACC GTGACCACGG GGATCGTCAG 1200  
CGCTCTCAAC CGTCCAGTGT CGACGACCGG CGAGGCCGGC AACCAGAACA CCGTGCTGGA 1260  
CGCCATTCAG ACCGACGCCG CGATCAACCC CGGTAATCC GGGGGCGCGC TGGTGAACAT 1320  
GAACGCTCAA CTCGTCGGAG TCAACTCGGC CATTGCCAGG CTGGGCGCGG ACTCAGCCGA 1380  
TGCGCAGAGC GGCTCGATCG GTCTCGGTTT TGCGATTCCA GTCGACCAGG CCAAGCGCAT 1440  
CGCCGACGAG TTGATCAGCA CCGGCAAGGC GTCACATGCC TCCCTGGGTG TGCAGGTGAC 1500  
CAATGACAA CAGACCCCG

CGCGGACGCG TTGGTTGCCG CCGTGCGGTC CAAAGCGCCG GGCGCCACGG TGGCGCTAAC 1680  
CTTTCAGGAT CCCTCGGGCG GTAGCCGCAC AGTGCAAGTC ACCCTCGGCA AGGCGGAGCA 1740  
GTGATGAAGG TCGCCGCGCA GTGTTCAAAG C 1771

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1058 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CTCCACCGCG GTGGCGGCCG CTCTAGAACT AGTGGATCCC CCGGGCTGCA GGAATTCGGC 60  
ACGAGGATCC GACGTGCGAG GTTGTGGAAC CCGCCGCCGC GGAAGTATCG GTCCATGCCT 120  
AGCCCGGCCA CGGCGAGCGC CGGAATGGCG CGAGTGAGGA GGCGGGCAAT TTGGCGGGGC 180  
CCGGCGACGG CGAGCGCCGG AATGGCGCGA GTGAGGAGGC GGCAGTCAT GCCAGCGTG 240  
ATCCAATCAA CCTGCATTCT GCCTGCGGGC CCATTTGACA ATCGAGGTAG TGAGCGCAAA 300  
TGAATGATGG AAAACGGGCG GTGACGTCCG CTGTTCTGGT GGTGCTAGGT GCCTGCCTGG 360  
CGTTGTGGCT ATCAGGATGT TCTTCGCCA AACCTGATGC CGAGGAACAG GGTGTTCCCG 420  
TGAGCCCGAC GCGTCCGAC CCGCGCTCC TCGCCGAGAT CAGGCAGTCG CTTGATGGCA 480

TGGGTATTAC CAGTGCCGAT GTCGACGTCC GGGCCAATCC GCTCGCGGCA AAGGGCGTAT 600  
GCACCTACAA CGACGAGCAG GGTGTCCCGT TTCGGGTACA AGGCGACAAC ATCTCGGTGA 660  
AACTGTTTGA CGACTGGAGC AATCTCGGCT CGATTTCTGA ACTGTCAACT TCACGCGTGC 720  
TCGATCCTGC CGCTGGGGTG ACGCAGCTGC TGTCCGGTGT CACGAACCTC CAAGCGCAAG 780  
GTACCGAAGT GATAGACGGA ATTTGACCA CAAAATCAC CGGGACCATC CCCGCGAGCT 840  
CTGTCAAGAT GCTTGATCCT GGCGCCAAGA GTGCAAGGCC GGCACCGTG TGGATTGCCC 900  
AGGACGGCTC GCACCACCTC GTCCGAGCGA GCATCGACCT CGGATCCGGG TCGATTGAGC 960  
TCACGCAGTC GAAATGGAAC GAACCCGTCA ACGTCGACTA GGCCGAAGTT GCGTCGACGC 1020  
GTTGNTCGAA ACGCCCTTGT GAACGGTGTC AACGGNAC 1058

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 542 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GAATTCGGCA CGAGAGGTGA TCGACATCAT CGGGACCAGC CCCACATCCT GGGAACAGGC 60  
GGCGGCGGAG GCGGTCCAGC GGGCGCGGGA TAGCGTCGAT GACATCCGCG TCGCTCGGGT 120

AAATCGCACG GTTTGCGGTT GATTCGTGCG ATTTTGTGTC TGCTCGCCGA GGCCTACCAG	300
GCGCGGCCCA GGTCCGCGTG CTGCCGTATC CAGGCGTGCA TCGCGATTCC GCGGGCCACG	360
CCGGAGTTAA TGCTTCGCGT CGACCCGAAC TGGGCGATCC GCCGGNGAGC TGATCGATGA	420
CCGTGGCCAG CCCGTGATG CCCGAGTTGC CCGAGGAAAC GTGCTGCCAG GCCGGTAGGA	480
AGCGTCCGTA GCGGCGGGTG CTGACCGGCT CTGCCTGCGC CCTCAGTGCG GCCAGCGAGC	540
GG	542

## (2) INFORMATION FOR SEQ ID NO:16:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 913 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CGGTGCCGCC CGCGCCTCG TTGCCCCCAT TGCCGCCGTC GCCGATCAGC TGCGCATCGC	60
CACCATCACC GCCTTTGCCG CCGGCACCGC CGGTGGCGCC GGGGCCCGCG ATGCCACCGC	120
TTGACCCTGG CGGCCGGGCG CGCCATTGCC ATACAGCACC CCGCCGGGGG CACCGTTACC	180
GCGTCGCCA CCGTCGCCG CGCTGCCGTT TCAGGCCGGG GAGGCCGAAT GAACCGCCGC	240
CAAGCCCGCC GCGGACCGG TTGCCGCTT TTCCGCCGCG CCGGCCGGCG CCGGCAATTC	300

GCCGCCGGAC CCGCCATTAC CGCCGTTCCC GTTCGGTGCC CCGCCGTTAC CGGCGCCGCC 420  
GTTTGCCGCC AATATTCGGC GGGCACC GCC AGACCCGCC GGGCCACCAT TGCCGCCGGG 480  
CACCGAAACA ACAGCCCAAC GGTGCCGCC GCGCCGCCGT TTGCCGCCAT CACCGGCCAT 540  
TCACCGCCAG CACCGCCGTT AATGTTTATG AACCCGGTAC CGCCAGCGCG GCCCCTATTG 600  
CCGGGCGCCG GAGNGCGTGC CCGCCGGCGC CGCCAACGCC CAAAAGCCCG GGGTTGCCAC 660  
CGGCCCCGCC GGACCCACCG GTCCCGCCA TCCCCCGTT GCCGCCGGTG CCGCCGCCAT 720  
TGGTGCTGCT GAAGCCGTTA GCGCCGTTT CCGCGGTTCC GCGGGTGGCG CCNTGGCCGC 780  
CGGCCCCGCC GTTGCCGTAC AGCCACCCCC CGGTGGCGCC GTTGCCGCCA TTGCCGCCAT 840  
TGCCGCCGTT GCCGCCATTG CCGCCGTTCC CGCCGCCACC GCCGGNTTGG CCGCCGGCGC 900  
CGCCGGCGGC CGC 913

## (2) INFORMATION FOR SEQ ID NO:17:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1872 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GACTACGTTG GTGTAGAAAA ATCCTGCCGC CCGACCCCTT AAGGCTGGGA CAATTTCTGA 60

GGCGGCCCG CCGGCCTTGT CGCAGGACCG GTTCGCCGAC TTCCCCGCGC TGCCCCCTCGA 240  
CCCGTCCGCG ATGGTCGCCC AAGTGGCGCC ACAGGTGGTC AACATCAACA CCAAAGTGGG 300  
CTACAACAAC GCCGTGGGCG CCGGGACCGG CATCGTCATC GATCCCAACG GTGTCGTGCT 360  
GACCAACAAC CACGTGATCG CGGGCGCCAC CGACATCAAT GCGTTCAGCG TCGGCTCCGG 420  
CCAAACCTAC GCGGTCGATG TGSTGGGTA TGACCGCACC CAGGATGTGCG CGGTGCTGCA 480  
GCTGCGCGGT GCCGGTGGCC TGCCGTCCGC GCGCATCGGT GCGGGCGTCG CGGTTGGTGA 540  
GCCCGTCGTC GCGATGGGCA ACAGCGGTGG GCAGGGCGGA ACGCCCCGTG CGGTGCCTGG 600  
CAGGGTGGTC GCGCTCGGCC AAACCGTGCA GCGGTCCGAT TCGCTGACCG GTGCCGAAGA 660  
GACATTGAAC GGGTTGATCC AGTTCGATGC CGCAATCCAG CCCGGTGATT CGGGCGGGCC 720  
CGTCGTCAAC GGCCTAGGAC AGGTGGTCGG TATGAACACG GCCGCGTCCG ATAACTTCCA 780  
GCTGTCCCAG GGTGGGCAGG GATTGCCAT TCCGATCGGG CAGGCGATGG CGATCGCGGG 840  
CCAAATCCGA TCGGGTGGGG GGTACCCAC CGTTCATATC GGGCCTACCG CCTTCCTCGG 900  
CTTGGGTGTT GTCGACAACA ACGGCAACGG CGCAGGAGTC CAACGCGTGG TCGGAAGCGC 960  
TCCGGCGGCA AGTCTCGGCA TCTCCACCGG CGACGTGATC ACCGCGGTGCG ACGGCGCTCC 1020  
GATCAACTCG GCCACCGCGA TGGCGGACGC GCTTAACGGG CATCATCCCG GTGACGTGAT 1080  
CTCGGTGAAC TGGCAAACCA AGTCGGGCGG CACGCGTACA GGAACGTGA CATGCGCCGA 1140



GCAATGAACG AGGCAGAACA CAGCGTTGAG CACCCTCCCG TGCAGGGCAG TTACGTCGAA 1320  
GGCGGTGTGG TCGAGCATCC GGATGCCAAG GACTTCGGCA GCGCCGCCGC CCTGCCCGCC 1380  
GATCCGACCT GGTTTAAGCA CGCCGTCTTC TACGAGGTGC TGGTCCGGGC GTTCTTCGAC 1440  
GCCAGCGCGG ACGGTTCCGN CGATCTGCGT GGACTCATCG ATCGCCTCGA CTACCTGCAG 1500  
TGGCTTGCCA TCGACTGCAT CTGTTGCCGC CGTTCCTACG ACTCACCGCT GCGCGACGGC 1560  
GGTTACGACA TTCGCGACTT CTACAAGGTG CTGCCCGAAT TCGGCACCGT CGACGATTTT 1620  
GTCGCCCTGG TCGACACCGC TCACCGGCGA GGTATCCGCA TCATCACCGA CCTGGTGATG 1680  
AATCACACCT CGGAGTCGCA CCCCTGGTTT CAGGAGTCCC GCCGCGACCC AGACGGACCG 1740  
TACGGTGA CTATTACGTGTG GAGCGACACC AGCGAGCGCT ACACCGACGC CCGGATCATC 1800  
TTCGTCGACA CCGAAGAGTC GAACTGGTCA TTCGATCCTG TCCGCCGACA GTTNCTACTG 1860  
GCACCGATTG TT 1872

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1482 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:18

CCGCGCTCCT CGCCGAGATC AGGCAGTCGC TTGATGCGAC AAAAGGGTTG ACCAGCGTGC	120
ACGTAGCGGT CCGAACAACC GGGAAAGTCG ACAGCTTGCT GGGTATTACC AGTGCCGATG	180
TCGACGTCCG GGCCAATCCG CTCGCGGCAA AGGGCGTATG CACCTACAAC GACGAGCAGG	240
GTGTCCCGTT TCGGGTACAA GGGGACAACA TCTCGGTGAA ACTGTTCGAC GACTGGAGCA	300
ATCTCGGCTC GATTTCTGAA CTGTCAACTT CACGCGTGCT CGATCCTGCC GCTGGGGTGA	360
CGCAGCTGCT GTCCGGTGTC ACGAACCTCC AAGCGCAAGG TACCGAAGTG ATAGACGGAA	420
TTTCGACCAC CAAAATCACC GGGACCATCC CCGCGAGCTC TGTCAGATG CTTGATCCTG	480
GCGCCAAGAG TGCAAGGCCG GCGACCGTGT GGATTGCCCA GGACGGCTCG CACCACCTCG	540
TCCGAGCGAG CATCGACCTC GGATCCGGGT CGATTCAGCT CACGCAGTCG AAATGGAACG	600
AACCCGTCAA CGTCGACTAG GCCGAAGTTG CGTCGACGCG TTGCTCGAAA CGCCCTTGTC	660
AACGGTGTCA ACGGCACCCG AAAACTGACC CCCTGACGGC ATCTGAAAAT TGACCCCTTA	720
GACCGGGCGG TTGGTGGTTA TTCTTCGGTG GTTCCGGCTG GTGGGACGCG GCCGAGGTCG	780
CGGTCTTTGA GCCGGTAGCT GTCGCCTTTG AGGGCGACGA CTTCAGCATG GTGGACGAGG	840
CGGTCGATCA TGGCGGCAGC AACGACGTCG TCGCCGCCGA AAACCTCGCC CCACCGGCCG	900
AAGGCCTTAT TGGACGTGAC GATCAAGCTG GCCCGCTCAT ACCGGGAGGA CACCAGCTGG	960
AAGAAGAGGT TGGCGGCCTC GGGCTCAAAC GGAATGTAAC CGACTTCGTC AACCACCAGG	1020
AGCGGATAGC GGCCAAACCG GGTGAGTTG GCGTAGATGC GCGCGGCGTG GTGAGCTCG	1080

GCGCGTATCG CCAGGCCGAC CGCAAGATGA GTCTTCCCGG TGCCAGGCGG GGCCCAAAAA 1200  
CACGACGTTA TCGCGGGCGG TGATGAAATC CAGGGTGCCC AGATGTGCGA TGGTGTGCGG 1260  
TTTGAGGCCA CGAGCATGCT CAAAGTCGAA CTCTTCCAAC GACTTCCGAA CCGGGAAGCG 1320  
GGCGGCGCGG ATGCGGCCCT CACCACCATG GGA CTCCCGG GCTGACACTT CCCGCTGCAG 1380  
GCAGGCGGCC AGGTATTCTT CGTGGCTCCA GTTCTCGGCG CGGGCGCGAT CGGCCAGCCG 1440  
GGACACTGAC TCACGCAGGG TGGGAGCTTT CAATGCTCTT GT 1482

## (2) INFORMATION FOR SEQ ID NO:19:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 876 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GAATTCGGCA CGAGCCGGCG ATAGCTTCTG GGCCGCGGCC GACCAGATGG CTCGAGGGTT 60  
CGTGCTCGGG GCCACGCGG GGGCACCAC CCTGACCGGT GAGGGCCTGC AACACGCCGA 120  
CGGTCACTCG TTGCTGCTGG ACGCCACCAA CCCGGCGGTG GTTGCTACG ACCCGGCTT 180  
CGCTACGAA ATCGGCTACA TCGNGGAAAG CGGACTGGCC AGGATGTGCG GGGAGAACCC 240  
GGAGAACATC TTCTTCTACA TCACGTCTA CAACGAGCCG TACGTGCAGC CGCCGAGCC 300

GGCAGCACAG ATGCTGGCCG CCGAGTGGGA TGTCGCCGCC GACGTGTGGT CGGTGACCAG 480  
 TTGGGGCGAG CTAACCCGCG ACGGGTGGT CATCGAGACC GAGAAGCTCC GCCACCCCGA 540  
 TCGGCCGGCG GCGGTGCCCT ACGTGACGAG AGCGCTGGAG AATGCTCGGG GCCCGGTGAT 600  
 CGCGGTGTCTG GACTGGATGC GCGCGGTCCC CGAGCAGATC CGACCGTGGG TGCCGGGCAC 660  
 ATACCTCACC TTGGGCACCG ACGGGTTCGG TTTTCCGAC ACTCGGCCCG CCGGTCTCTG 720  
 TTACTTCAAC ACCGACGCCG AATCCCAGGT TGGTCGCGGT TTTGGGAGGG GTTGGCCGGG 780  
 TCGACGGGTG AATATCGACC CATTGGTGC CGGTCGTGGG CCGCCCGCCC AGTTACCCGG 840  
 ATTCGACGAA GGTGGGGGGT TCGCCCCGAN TAAGTT 876

## (2) INFORMATION FOR SEQ ID NO:20:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1021 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

ATCCCCCGG GCTGCAGGAA TTCGGCACGA GAGACAAAAT TCCACGCGTT AATGCAGGAA 60  
 CAGATTCATA ACGAATTCAC AGCGGCACAA CAATATGTCTG CGATCGCGGT TTATTTCTGAC 120  
 AGCGAAGACC TGCCGCAGTT GCGGAAGCAT TTTTACAGCG ACGCGCTCGG GCGGACGAG

GTAGACACGG TCGGAAACCA GTTCGACAGA CCCC GCGAGG CACTGGCGCT GGCGCTCGAT 300  
CAGGAACGCA CAGTCACCGA CCAGGTCGGT CGGCTGACAG CGGTGGCCCG CGACGAGGGC 360  
GATTTCTCTG GCGAGCAGTT CATGCASTGG TTCTTGACAG AACAGATCGA ACAGGTGGCC 420  
TTGATGGCAA CCCTGGTGCG GGTGCGGAT CGGGCCGGGG CCAACCTGTT CGAGCTAGAG 480  
AACTTCGTCTG CACGTGAAGT GGATGTGGCG CCGGCCGCAT CAGGCGCCCC GCACGCTGCC 540  
GGGGGCCGCC TCTAGATCCC TGGGGGGGAT CAGCGAGTGG TCCCGTTCGC CCGCCCGTCT 600  
TCCAGCCAGG CCTTGGTGCG GCCGGGGTGG TGAGTACCAA TCCAGGCCAC CCCGACCTCC 660  
CGGNAAAAGT CGATGTCCTC GTACTCATCG ACGTTCCAGG AGTACACCGC CCGGCCCTGA 720  
GCTGCCGAGC GGTCAACGAG TTGCGGATAT TCCTTTAACG CAGGCAGTGA GGGTCCCACG 780  
GCGGTTGGCC CGACCGCCGT GGCCGCACTG CTGGTCAGGT ATCGGGGGGT CTTGGCGAGC 840  
AACAACGTCTG GCAGGAGGGG TGGAGCCCGC CGGATCCGCA GACCGGGGGG GCGAAAACGA 900  
CATCAACACC GCACGGGATC GATCTGCGGA GGGGGGTGCG GGAATACCGA ACCGGTGTAG 960  
GAGCGCCAGC AGTTGTTTTT CCACCAGCGA AGCGTTTTCG GGTCATCGGN GGCNNTTAAG 1020  
T 1021

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 321 base pairs

(B) TYPE: nucleic acid

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CGTGCCGACG AACGGAAGAA CACAACCATG AAGATGGTGA AATCGATCGC CGCAGGTCTG	60
ACCGCCGCGG CTGCAATCGG CGCCGCTGCG GCCGGTGTGA CTTCGATCAT GGCTGGCGGN	120
CCGGTCGTAT ACCAGATGCA GCCGGTCGTC TTCGGCGCGC CACTGCCGTT GGACCCGGNA	180
TCCGCCCTG ANGTCGGAC CGCCCCCAG TGGACCAGNC TGCTCAACAG NCTGNCGAT	240
CCCAACGTGT CGTTTGNGAA CAAGGGNAGT CTGGTCGAGG GNNGNATCGG NGGNANCGAG	300
GGNGNGNATC GNCGANACA A	321

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 373 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

TCTTATCGGT TCCGGTTGGC GACGGGTTTT GGGNGCGGGT GGTAAACCG CTCGGCCAGC	60
CGATCGACGG GCGCGGAGAC GTCGACTCCG ATACTCGGCG CGCGCTGGAG CTCCAGGCGC	120
CCTCGGTGGT GNACCGGCAA GCGGTGAAGG AGCCGTTGNA GACCGGGATC AAGGCGATTG	180
ACGCGATGAC CCGATCGGC CGCGGGCAGC GCCAGCTGAT CATCGGGAG CGCAAGACCG	240

GGTGGATCCC AAGAAGCAGG TCGCTTGTG TATACGTTGG CCATCGGGCA AGAAGGGGAA 360

CTTACCATCG CCG 373

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 352 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GTGACGCCGT GATGGGATTC CTGGGCGGGG CCGGTCCGCT GGCGGTGGTG GATCAGCAAC 60

TGGTTACCCG GGTGCCGCAA GGCTGGTCGT TTGCTCAGGC AGCCGCTGTG CCGGTGGTGT 120

TCTTGACGGC CTGGTACGGG TTGGCCGATT TAGCCGAGAT CAAGGCGGGC GAATCGGTGC 180

TGATCCATGC CCGTACCGGC GGTGTGGGCA TGGCGGCTGT GCAGCTGGCT CGCCAGTGGG 240

GCGTGGAGGT TTTCGTCACC GCCAGCCGTG GNAAGTGGGA CACGCTGCGC GCCATNGNGT 300

TTGACGACGA NCCATATCGG NGATTCCNC ACATNCGAAG TTCCGANGGA GA 352

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 726 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GAAATCCGCG TTCATTCCGT TCGACCAGCG GCTGGCGATA ATCGACGAAG TGATCAAGCC	60
GCGGTTTCGCG GCGCTCATGG GTCACAGCGA GTAATCAGCA AGTTCTCTGG TATATCGCAC	120
CTAGCGTCCA GTTGCTTGCC AGATCGCTTT CGTACCGTCA TCGCATGTAC CGGTTTCGCGT	180
GCCGCACGCT CATGCTGGCG GCGTGCATCC TGGCCACGGG TGTGGCGGGT CTCGGGGTCG	240
GCGCGCAGTC CGCAGCCCAA ACCGCGCCGG TGCCCGACTA CTA CTGGTGC CCGGGGCAGC	300
CTTTCGACCC CGCATGGGGG CCCAACTGGG ATCCCTACAC CTGCCATGAC GACTTCCACC	360
GCGACAGCGA CGGCCCCGAC CACAGCCGCG ACTACCCCGG ACCCATCCTC GAAGGTCCCG	420
TGCTTGACGA TCCCGGTGCT GCGCCGCCGC CCCCGGCTGC CGGTGGCGG GCATAGCGCT	480
CGTTGACCGG GCCGCATCAG CGAATACGCG TATAAACCCG GCGTGCCCC CGGCAAGCTA	540
CGACCCCGG CGGGGCAGAT TTACGCTCCC GTGCCGATGG ATCGCGCCGT CCGATGACAG	600
AAAATAGGCG ACGGTTTTGG CAACCGCTTG GAGGACGCTT GAAGGGAACC TGTCATGAAC	660
GGCGACAGCG CCTCCACCAT CGACATCGAC AAGGTTGTTA CCCGCACACC CGTTCGCCGG	720
ATCGTG	726

## (2) INFORMATION FOR SEQ ID NO:25:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 580 base pairs

(B) TYPE: nucleic acid



## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CGCGACGACG ACGAACGTCG GGCCACCAC CGCCTATGCG TTGATGCAGG CGACCGGGAT	60
GGTCGCCGAC CATATCCAAG CATGCTGGGT GCCCACTGAG CGACCTTTTG ACCAGCCGGG	120
CTGCCCAGTG GCGGCCCGGT GAAGTCATTG CGCCGGGGCT TGTGCACCTG ATGAACCCGA	180
ATAGGGAACA ATAGGGGGGT GATTGGCAG TTCAATGTG GGTATGGCTG GAAATCCAAT	240
GGCGGGGCAT GCTCGGCCG GACCAGGCTC GCGCAGGCGG GCCAGCCCGA ATCTGGAGGG	300
AGCACTCAAT GCGGCGGATG AAGCCCCGGA CCGGCGACGG TCCTTTGGAA GCAACTAAGG	360
AGGGGCGCGG CATTGTGATG CGAGTACCAC TTGAGGGTGG CGGTCGCCTG GTCGTCGAGC	420
TGACACCCGA CGAAGCCGCC GCACTGGGTG ACGAACTCAA AGGCGTTACT AGCTAAGACC	480
AGCCCAACGG CGAATGGTCG GCGTTACGCG CACACCTTCC GGTAGATGTC CAGTGTCTGC	540
TCGGCGATGT ATGCCAGGA GAACTCTTGG ATACAGCGCT	580

## (2) INFORMATION FOR SEQ ID NO:26:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 160 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GGTACCGCCG GGTGTTCGG TGTCGGCGGG GCCGGTGGGG CCGGAGGCAA CGGCATCGCC 120

GGTGTACCG GTACGTCGGC CAGCACACCG GGTGGATCCG 160

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 272 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GACACCGATA CGATGGTGAT GTACGCCAAC GTTGTGACA CGCTCGAGGC GTTCACGATC 60

CAGCGCACAC CCGACGGCGT GACCATCGGC GATGCGGCC CGTTCGCGGA GCGGGCTGCC 120

AAGGCGATGG GAATCGACAA GCTGCGGGTA ATTCATACCG GAATGGACCC CGTCGTCGCT 180

GAACGCGAAC AGTGGGACGA CGGCAACAAC ACGTTGGCGT TGGCGCCCGG TGTCGTTGTC 240

GCCTACGAGC GCAACGTACA GACCAACGCC CG 272

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 317 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

GCAGCCGGTG GTTCTCGGAC TATCTGCGCA CGGTGACGCA GCGCGACGTG CGCGAGCTGA 60  
AGCGGATCGA GCAGACGGAT CGCCTGCCGC GGTTCATGCG CTACCTGGCC GCTATCACCG 120  
CGCAGGAGET GAACGTGGCC GAAGCGGCGC GGGTCATCGG GGTGACGCG GGGACGATCC 180  
GTTGCGATCT GCGTGGTTC GAGACGGTCT ATCTGGTACA TCGCCTGCCC GCCTGGTCGC 240  
GGAATCTGAC CGCGAAGATC AAGAAGCGGT CAAAGATCCA CGTCGTCGAC AGTGGCTTCG 300  
CGGCCTGGTT GCGCGGG 317

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 182 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GATCGTGGAG CTGTGATGA ACAGCGTTGC CGGACGCGCG GCGGCCAGCA CGTCGGTGTA 60  
GCAGCGCCGG ACCACCTCGC CGGTGGGCAG CATGGTGATG ACCACGTGCG CCTCGGCCAC 120  
CGCTTCGGGC GCGCTACGAA ACACGCGGAC ACCGTGCGCG GCGGCGCCGG ACGCCGCCGT 180  
GG 182

(2) INFORMATION FOR SEQ ID NO:30:

(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GATCGCGAAG TTTGGTGAGC AGGTGGTCGA CGCGAAAGTC TGGGCGCCTG CGAAGCGGGT	60
CGGCGTTCAC GAGGCGAAGA CACGCTGTC CGAGCTGCTG CGGCTCGTCT ACGGCGGGCA	120
GAGGTTGAGA TTGCCCGCCG CGGCGAGCCG GTAGCAAAGC TTGTGCCGCT GCATCCTCAT	180
GAGACTCGGC GGTTAGGCAT TGACCATGGC GTGTACCGCG TGCCCGACGA TTTGGACGCT	240
CCGTTGTCAG ACGACGTGCT CGAACGCTTT CACCGGTGAA GCGCTACCTC ATCGACACCC	300
ACGTTTGG	308

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 267 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CCGACGACGA GCAACTCACG TGGATGATGG TCGGCAGCGG CATTGAGGAC GGAGAGAATC	60
CGGCCGAAGC TGCCGCGCGG CAAGTGCTCA TAGTGACCGG CCGTAGAGGG CTCCCCGAT	120
GGCACCAGAC TATTCTGGT TCCCGCTCCG CCGTACAGC CCGTACAGC	

TCGACGCGGC AATCCAGGGC GGTCTGG

267

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 189 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CTCGTGCCGA AGAATGTGA GGGGACACGA TGAGCAATCA CACCTACCGA GTGATCGAGA 60

TCGTGCGGAC CTCGCCCAC GCGTCGACG CGGCAATCCA GGGCGGTCTG GCGCGAGCTG 120

GCGAGACCAT GCGCGCGCTG GACTGGTTCG AAGTACAGTC AATTCGAGGC CACCTGGTCG 180

ACGGAGCGG 189

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 851 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CTGCAGGGTG GCGTGGATGA GCGTCACCGC GGGGCAGGCC GAGGTGACCG CCGCCCCAGGT 60

CGCCGAGAAC CGTGCTGAAC TGATGATTCT GATAGCGACC AACCTCTTGG GGCAAAACAC 180  
CCCGGCGATC GCGGTCAACG AGGCCGAATA CGGCGAGATG TGGGCCCAAG ACGCCGCCGC 240  
GATGTTTGGC TACGCCGCGG CGACGGCGAC GGCGACGGCG ACGTTGCTGC CGTTCGAGGA 300  
GGCGCCGGAG ATGACCAGCG CGGGTGGGCT CCTCGAGCAG GCCGCCGCGG TCGAGGAGGC 360  
CTCCGACACC GCCGCGGCGA ACCAGTTGAT GAACAATGTG CCCCAGGCGC TGAAACAGTT 420  
GGCCAGCCC ACGCAGGGCA CCACGCCTTC TTCCAAGCTG GGTGGCCTGT GGAAGACGGT 480  
CTCGCCGCAT CGGTGCGCGA TCAGCAACAT GGTGTCGATG GCCAACAACC ACATGTCGAT 540  
GACCAACTCG GGTGTGTCGA TGACCAACAC CTTGAGCTCG ATGTTGAAGG GCTTTGCTCC 600  
GGCGGCGGCC GCCCAGGCCG TGCAAACCGC GGCGCAAAAC GGGGTCCGGG CGATGAGCTC 660  
GCTGGGCAGC TCGCTGGGT CTTCGGGTCT GGGCGGTGGG GTGGCCGCCA ACTTGGGTGC 720  
GGCGGCCTCG GTACGGTATG GTCACCGGGA TGGCGGAAAA TATGCANAGT CTGGTCGGCG 780  
GAACGGTGGT CCGGCGTAAG GTTTACCCCC GTTTTCTGGA TCGGTGAAC TTCGTCAACG 840  
GAAACAGTTA C 851

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 254 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

GATCGATCGG GCGGAAATTT GGACCAGATT CGCCTCCGGC GATAACCCAA TCAATCGAAC 60  
CTAGATTTAT TCCGTCCAGG GGCCCGAGTA ATGGCTCGCA GGAGAGGAAC CTTACTGCTG 120  
CGGGCACCTG TCGTAGGTCC TCGATACGGC GGAAGGCGTC GACATTTTCC ACCGACACCC 180  
CCATCCAAAC GTTCGAGGGC CACTCCAGCT TGTGAGCGAG GCGACGCAGT CGCAGGCTGC 240  
GCTTGGTCAA GATC 254

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 408 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CGGCACGAGG ATCCTGACCG AAGCGGCCGC CGCCAAGGCG AAGTCGCTGT TGGACCAGGA 60  
GGGACGGGAC GATCTGGCSC TCGGATCGC GGTTCAGCCG GGGGGGTGCG CTGGATTGCG 120  
CTATAACCTT TTCTTCGACG ACCGGACGCT GGATGGTGAC CAAACCGCGG AGTTCGGTGG 180  
TGTCAGGTTG ATCGTGGACC GGATGAGCGC GCCGTATGTG GAAGGCGCGT CGATCGATTT 240  
CGTCGACACT ATTGAGAAGC AAGGNTTCAC CATCGACAAT CCCAACGCCA CCGGCTCCTG 300  
CGCGTGCGGG GATTCGTTCA ACTGATAAAA CGCTAGTAGG ACCCGCGGT GCGCAACAGG 360

## (2) INFORMATION FOR SEQ ID NO:36:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 181 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

```
GCGGTGTCGG CGGATCCGGC GGGTGGTTGA ACGGCAACGG CGGGGCCGGC GGGGCCGGCG      60
GGACCGGGCG TAACGGTGGT GCCGGCGGCA ACGCCTGGTT GTTCGGGGCC GCGGGGTCCG      120
GCGGNGCCGG CACCAATGGT GNGTCGGCG GGTCCGGCGG ATTTGTCTAC GGCAACGGCG      180
G                                                                              181
```

## (2) INFORMATION FOR SEQ ID NO:37:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 290 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

```
GCGGTGTCGG CGGATCCGGC GGGTGGTTGA ACGGCAACGG CGGTGTCGGC GGCCGGGGCG      60
GCGACGGCGT CTTTGCCGGT GCCGGCGGCC AGGGCGGGCT CGGTGGGTAG GGCGGCAATG      120
```



CCCCGGACGG CGGCTTCGGT GGCAACGGCG GTAAGGGTGG CCAGGGCGGN ATTGGCGGCG 240  
GCACTCAGAG CGCGACCGGC CTCGGNGGTG ACGGCGGTGA CGGCGGTGAC 290

(2) INFORMATION FOR SEQ ID NO:38:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 34 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

GATCCAGTGG CATGGNGGGT GTCAGTGGAA GCAT 34

(2) INFORMATION FOR SEQ ID NO:39:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 155 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GATCGTGCT CGTCCCCCCC TTGCCGCCGA CGCCACCGGT CCCACCGTTA CCGAACAAGC 60  
TGGCGTGGTC GCCAGCACCC CCGGCACCGC CGACGCCGGA GTCGAACAAT GGCACCGTCG 120  
TATCCCCACC ATTGCCGCCG GNCCACCGG CACCG

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 53 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

ATGGCGTTCA CGGGGCGCCG GGGACCGGGC AGCCCGGNGG GGCCGGGGGG TGG

53

## (2) INFORMATION FOR SEQ ID NO:41:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 132 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GATCCACCGC GGGTGCAGAC GGTGCCCCGCG GCGCCACCCC GACCAGCGGC GGCAACGGCG

60

GCACCGGCGG CAACGGCGCG AACGCCACCG TCGTCGGNGG GGCCGGCGGG GCCGGCGGCA

120

AGGGCGGCAA CG

132

## (2) INFORMATION FOR SEQ ID NO:42:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 132 base pairs
- (B) TYPE: nucleic acid

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

GATCGGCGGC CCGNACGGNC GGGGACGGCG GCAAGGGCGG NAACGGGGGC GCCGNAGCCA 60  
CCNGCCAAGA ATCCTCCGNG TCCNCCAATG GCGCGAATGG CGGACAGGGC GGCAACGGCG 120  
GCANCGGCGG CA 132

## (2) INFORMATION FOR SEQ ID NO:43:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 702 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CGGCACGAGG ATCGGTACCC CGCGGCATCG GCAGCTGCCG ATTCGCCGGG TTTCCCACC 60  
CGAGGAAAGC CGCTACCAGA TGGCGTGCC GAAGTAGGGC GATCCGTTCC CGATGCCGGC 120  
ATGAACGGGC GGCATCAAAT TAGTGCAGGA ACCTTTCAGT TTAGCGACGA TAATGGCTAT 180  
AGCACTAAGG AGGATGATCC GATATGACGC AGTCGCAGAC CGTGACGGTG GATCAGCAAG 240  
AGATTTTGAA CAGGGCCAAC GAGGTGGAGG CCCCATGGC GGACCCACCG ACTGATGTCC 300  
CCATCACACC GTGCGAACTC ACGGNGGNTA AAAACGCCGC CCAACAGNTG GTNTTGTCG 360  
CCGACAACAT GCGGGAATAC CTGGCGGCGG GTGCCAAGA GCGGCAGCGT CTGGCGACCT 420

ACAACGACGG CGAAGGAACT GTGCAGGCAG AATCGGCCGG GGCCGTCGGA GGGGACAGTT 540  
 CGGCCGAACT AACCGATACG CCGAGGGTGG CCACGGCCGG TGAACCCAAC TTCATGGATC 600  
 TCAAAGAAGC GGCAAGGAAG CTCGAAACGG GCGACCAAGG CGCATCGCTC GCGCACTGNG 660  
 GGGATGGGTG GAACACTTNC ACCCTGACGC TGCAAGGCGA CG 702

## (2) INFORMATION FOR SEQ ID NO:44:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 298 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GAAGCCGCAG CGCTGTCGGG CGACGTGGCG GTCAAAGCGG CATCGCTCGG TGGCGGTGGA 60  
 GGCGGCGGGG TGCCGTCGGC GCCGTTGGGA TCCGCGATCG GGGGCGCCGA ATCGGTGCGG 120  
 CCCGCTGGCG CTGGTGACAT TGCCGGCTTA GSCCAGGGAA GGGCCGGCGG CGGCGCCGCG 180  
 CTGGGCGGCG GTGGCATGGG AATGCCGATG GGTGCCGCGC ATCAGGGACA AGGGGGCGCC 240  
 AAGTCCAAGG GTTCTCAGCA GGAAGACGAG GCGCTCTACA CCGAGGATCC TCGTGCCG 298

## (2) INFORMATION FOR SEQ ID NO:45:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1058 base pairs

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CGGCACGAGG ATCGAATCGC GTCGCCGGGA GCACAGCGTC GCACTGCACC AGTGGAGGAG	60
CCATGACCTA CTCGCCGGGT AACCCCGGAT ACCCGCAAGC GCAGCCCGCA GGCTCCTACG	120
GAGGCGTCAC ACCCTCGTTC GCCCAGCCG ATGAGGGTGC GAGCAAGCTA CCGATGTACC	180
TGAACATCGC GGTGGCAGTG CTCGGTCTGG CTGCGTACTT CGCCAGCTTC GGCCCAATGT	240
TCACCCTCAG TACCGAACTC GGGGGGGGTG ATGGCGCAGT GTCCGGTGAC ACTGGGCTGC	300
CGGTCGGGGT GGCTCTGCTG GCTGCGCTGC TTGCCGGGT GGTCTGGTG CCTAAGGCCA	360
AGAGCCATGT GACGGTAGTT GCGGTGCTCG GGGTACTCGG CGTATTTCTG ATGGTCTCGG	420
CGACGTTTAA CAAGCCCAGC GCCTATTCGA CCGGTTGGGC ATTGTGGGT GTGTTGGCTT	480
TCATCGTGTT CCAGGCGGTT GCGGCAGTCC TGGCGTCTT GGTGGAGACC GGCGCTATCA	540
CCGCGCCGGC GCCGCGGCC AAGTTCGACC CGTATGGACA GTACGGGCGG TACGGGCAGT	600
ACGGGCAGTA CGGGGTGCAG CCGGTGGGT ACTACGGTCA GCAGGGTGCT CAGCAGGCCG	660
CGGGA CTGCA GTCGCCCGGC CCGCAGCAGT CTCGCAGCC TCCCGGATAT GGGTCGCAGT	720
ACGGCGGCTA TTCGTCCAGT CCGAGCCAAT CGGGCAGTGG ATACACTGCT CAGCCCCCGG	780
CCCAGCCGCC GGCAGTCC GGGTCGCAAC AATCGCACCA GGGCCCATCC ACGCCACCTA	840
CCGGCTTTCC GAGCTTCAGC GCACGACAG GGTGAGTCC GGGGCGGCTT TGAATG	

GGGCGCCGGT CTAACCGGGC GTTCCCGCGT CCGGTCGCGC GTGTGCGCGA AGAGTGAACA 1020  
GGGTGTCAGC AAGCGCGGAC GATCCTCGTG CCGAATTC 1058

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 327 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CGGCACGAGA GACCGATGCC GCTACCCTCG CGCAGGAGGC AGGTAATTTT GAGCGGATCT 60  
CCGGCGACCT GAAAACCCAG ATCGACCAGG TGGAGTCGAC GGCAGGTTTC TTGCAGGGCC 120  
AGTGGCGCGG CGCGGCGGGG ACGGCCGCCC AGGCCGCGGT GGTGCGCTTC CAAGAAGCAG 180  
CCAATAAGCA GAAGCAGGAA CTCGACGAGA TCTCGACGAA TATTCGTCAG GCCGGCGTCC 240  
AATACTCGAG GGCCGACGAG GAGCAGCAGC AGGCGCTGTC CTCGCAAATG GGCTTCTGAC 300  
CCGCTAATAC GAAAAGAAAC GGAGCAA 327

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

CGGTCGCGAT GATGGCGTTG TCGAACGTGA CCGATTCTGT ACCGCCGTCG TTGAGATCAA 60  
CCAACAACGT GTTGGCGTCG GCAAATGTGC CGNACCCGTG GATCTCGGTG ATCTTGTCT 120  
TCTTCATCAG GAAGTGCACA CCGGCCACCC TGCCCTCGGN TACCTTTCGG 170

## (2) INFORMATION FOR SEQ ID NO:48:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 127 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GATCCGGCGG CACGGGGGGT GCCGGCGGCA GCACCGCTGG CGCTGGCGGC AACGGCGGGG 60  
CCGGGGGTGG CGGCGGAACC GGTGGGTTGC TCTTCGGCAA CGGCGGTGCC GCGGGGCACG 120  
GGGCCGT 127

## (2) INFORMATION FOR SEQ ID NO:49:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 81 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

CGGCGGCAAG GGCGGCACCG CCGGCAACGG GAGCGGCGCG GCCGGCGGCA ACGGCGGCAA 60

CGGCGGCTCC GGCTCAACG G 81

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 149 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

GATCAGGGCT GGCCGGCTCC GGCCAGAAGG GCGGTAACGG AGGAGCTGCC GGATTGTTTG 60

GCAACGGCGG GGCCGGNGGT GCCGGCGCGT CCAACCAAGC CGGTAACGGC GGNGCCGGCG 120

GAAACGGTGG TGCCGGTGGG CTGATCTGG 149

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 355 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

CGGCACGAGA TCACACCTAC CGAGTGATCG AGATGTCGG GAGCTGGCGG GAGGCTCTCG 60



TCGAAGTACA GTCAATTCTGA GGCCACCTGG TCGACGGAGC GGTCGCGCAC TTCCAGGTGA 180  
CTATGAAAGT CGGCTTCCGC CTGGAGGATT CCTGAACCTT CAAGCGCGGC CGATAACTGA 240  
GGTGCATCAT TAAGCGACTT TTCCAGAACA TCCTGACGCG CTCGAAACGC GGTTCAGCCG 300  
ACGGTGGCTC CGCCGAGGCG CTGCCTCCAA AATCCCTGCG ACAATTCGTC GGCGG 355

## (2) INFORMATION FOR SEQ ID NO:52:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 999 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ATGCATCACC ATCACCATCA CATGCATCAG GTGGACCCCA ACTTGACACG TCGCAAGGGA 60  
CGATTGGCGG CACTGGCTAT CGCGGCGATG GCCAGCGCCA GCCTGGTGAC CGTTGCGGTG 120  
CCCGCGACCG CCAACGCCGA TCCGGAGCCA GCGCCCCCGG TACCCACAAC GGCCGCCTCG 180  
CCGCCGTCTGA CCGCTGCAGC GCCACCCGCA CCGGCGACAC CTGTTGCCCC CCCACCAACG 240  
GCCGCCGCCA ACACGCCGAA TGCCAGCCG GCGATCCCA ACGCAGCACC TCCGCCGGCC 300  
GACCCGAACG CACCGCCGCC ACCTGTCATT GCCCCAAACG CACCCCAACC TGTCCGGATC 360  
GACAACCCGG TTGGAGGATT CAGCTTCGCG CTGCCTGCTG GCTGGGTGGA GTCTGACGCC 420

CTTTACGCCA GCGCCGAAGC CACCGACTCC AAGGCCGCGG CCCGGTTGGG CTCGGACATG 600  
 GGTGAGTTCT ATATGCCCTA CCCGGGCACC CGGATCAACC AGGAAACCGT CTCGCTCGAC 660  
 GCCAACGGGG TGTCTGGAAG CGCGTCGTAT TACGAAGTCA AGTTCAGCGA TCCGAGTAAG 720  
 CCGAACGGCC AGATCTGGAC GGGCGTAATC GGCTCGCCCG CGGCGAACGC ACCGGACGCC 780  
 GGGCCCCCTC AGCGCTGGTT TGTGCTATGG CTCGGGACCG CCAACAACCC GGTGGACAAG 840  
 GGCGCGGCCA AGGCGCTGGC CGAATCGATC CGGCCTTTGG TCGCCCCGCC GCCGGCGCCG 900  
 GCACCGGCTC CTGCAGAGCC CGCTCCGGCG CCGGCGCCGG CCGGGGAAGT CGCTCCTACC 960  
 CCGACGACAC CGACACCGCA GCGGACCTTA CCGGCCTGA 999

## (2) INFORMATION FOR SEQ ID NO:53:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 332 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (x1) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Met His His His His His His Met His Gln Val Asp Pro Asn Leu Thr  
 1 5 10 15  
 Arg Arg Lys Gly Arg Leu Ala Ala Leu Ala Ile Ala Ala Met Ala Ser  
 20 25 30

Glu Pro Ala Pro Pro Val Pro Thr Thr Ala Ala Ser Pro Pro Ser Thr  
50 55 60

Ala Ala Ala Pro Pro Ala Pro Ala Thr Pro Val Ala Pro Pro Pro Pro  
65 70 75 80

Ala Ala Ala Asn Thr Pro Asn Ala Gln Pro Gly Asp Pro Asn Ala Ala  
85 90 95

Pro Pro Pro Ala Asp Pro Asn Ala Pro Pro Pro Pro Val Ile Ala Pro  
100 105 110

Asn Ala Pro Gln Pro Val Arg Ile Asp Asn Pro Val Gly Gly Phe Ser  
115 120 125

Phe Ala Leu Pro Ala Gly Trp Val Glu Ser Asp Ala Ala His Phe Asp  
130 135 140

Tyr Gly Ser Ala Leu Leu Ser Lys Thr Thr Gly Asp Pro Pro Phe Pro  
145 150 155 160

Gly Gln Pro Pro Pro Val Ala Asn Asp Thr Arg Ile Val Leu Gly Arg  
165 170 175

Leu Asp Gln Lys Leu Tyr Ala Ser Ala Glu Ala Thr Asp Ser Lys Ala  
180 185 190

Ala Ala Arg Leu Gly Ser Asp Met Gly Glu Phe Tyr Met Pro Tyr Pro  
195 200 205

Gly Thr Arg Ile Asn Gln Glu Thr Val Ser Leu Asp Ala Asn Gly Val  
210 215 220

Pro Asn Gly Gln Ile Trp Thr Gly Val Ile Gly Ser Pro Ala Ala Asn  
                     245                    250                    255

Ala Pro Asp Ala Gly Pro Pro Gln Arg Trp Phe Val Val Trp Leu Gly  
                     260                    265                    270

Thr Ala Asn Asn Pro Val Asp Lys Gly Ala Ala Lys Ala Leu Ala Glu  
                     275                    280                    285

Ser Ile Arg Pro Leu Val Ala Pro Pro Pro Ala Pro Ala Pro Ala Pro  
                     290                    295                    300

Ala Glu Pro Ala Pro Ala Pro Ala Pro Ala Gly Glu Val Ala Pro Thr  
                     305                    310                    315                    320

Pro Thr Thr Pro Thr Pro Gln Arg Thr Leu Pro Ala  
                     325                    330

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Asp Pro Val Asp Ala Val Ile Asn Thr Thr Xaa Asn Tyr Gly Gln Val  
   1                    5                    10                    15

## (2) INFORMATION FOR SEQ ID NO:55:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Ala	Val	Glu	Ser	Gly	Met	Leu	Ala	Leu	Gly	Thr	Pro	Ala	Pro	Ser
1				5					10					15

## (2) INFORMATION FOR SEQ ID NO:56:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Ala	Ala	Met	Lys	Pro	Arg	Thr	Gly	Asp	Gly	Pro	Leu	Glu	Ala	Ala	Lys
1				5					10						15

Glu Gly Arg

## (2) INFORMATION FOR SEQ ID NO:57:

- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Tyr	Tyr	Trp	Cys	Pro	Gly	Gln	Pro	Phe	Asp	Pro	Ala	Trp	Gly	Pro
1				5					10				15	

(2) INFORMATION FOR SEQ ID NO:58:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 14 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Asp	Ile	Gly	Ser	Glu	Ser	Thr	Glu	Asp	Gln	Gln	Xaa	Ala	Val
1				5					10				

(2) INFORMATION FOR SEQ ID NO:59:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 13 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS:
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

## (2) INFORMATION FOR SEQ ID NO:60:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Asp Pro Glu Pro Ala Pro Pro Val Pro Thr Ala Ala Ala Ala Pro Pro  
1                      5                      10                      15

Ala

## (2) INFORMATION FOR SEQ ID NO:61:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Ala Pro Lys Thr Tyr Xaa Glu Glu Leu Lys Gly Thr Asp Thr Gly  
1                      5                      10                      15

## (2) INFORMATION FOR SEQ ID NO:62

(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Asp	Pro	Ala	Ser	Ala	Pro	Asp	Val	Pro	Thr	Ala	Ala	Gln	Gln	Thr	Ser
1				5					10					15	
Leu	Leu	Asn	Asn	Leu	Ala	Asp	Pro	Asp	Val	Ser	Phe	Ala	Asp		
				20				25					30		

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 24 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS:  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Gly	Cys	Gly	Asp	Arg	Ser	Gly	Gly	Asn	Leu	Asp	Gln	Ile	Arg	Leu	Arg
1					5				10					15	
Arg	Asp	Arg	Ser	Gly	Gly	Asn	Leu								
				20											

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS



(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Thr	Gly	Ser	Leu	Asn	Gln	Thr	His	Asn	Arg	Arg	Ala	Asn	Glu	Arg	Lys
1				5					10					15	
Asn	Thr	Thr	Met	Lys	Met	Val	Lys	Ser	Ile	Ala	Ala	Gly	Leu	Thr	Ala
			20					25					30		
Ala	Ala	Ala	Ile	Gly	Ala	Ala	Ala	Ala	Gly	Val	Thr	Ser	Ile	Met	Ala
			35					40					45		
Gly	Gly	Pro	Val	Val	Tyr	Gln	Met	Gln	Pro	Val	Val	Phe	Gly	Ala	Pro
		50					55						60		
Leu	Pro	Leu	Asp	Pro	Ala	Ser	Ala	Pro	Asp	Val	Pro	Thr	Ala	Ala	Gln
65						70						75			80
Leu	Thr	Ser	Leu	Leu	Asn	Ser	Leu	Ala	Asp	Pro	Asn	Val	Ser	Phe	Ala
					85						90				95
Asn	Lys	Gly	Ser	Leu	Val	Glu	Gly	Gly	Ile	Gly	Gly	Thr	Glu	Ala	Arg
					100							105			110
Ile	Ala	Asp	His	Lys	Leu	Lys	Lys	Ala	Ala	Glu	His	Gly	Asp	Leu	Pro
					115								125		
Leu	Ser	Phe	Ser	Val	Thr	Asn	Ile	Gln	Pro	Ala	Ala	Ala	Gly	Ser	Ala
														130	
														135	
															140
Thr	Ala	Asp	Val	Ser	Val	Ser	Gly	Pro	Lys	Leu	Ser	Ser	Pro	Val	Thr

100

Gln Asn Val Thr Phe Val Asn Gln Gly Gly Trp Met Leu Ser Arg Ala  
 165 170 175

Ser Ala Met Glu Leu Leu Gln Ala Ala Gly Xaa  
 180 185

## (2) INFORMATION FOR SEQ ID NO:65:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 148 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Asp Glu Val Thr Val Glu Thr Thr Ser Val Phe Arg Ala Asp Phe Leu  
 1 5 10 15

Ser Glu Leu Asp Ala Pro Ala Gln Ala Gly Thr Glu Ser Ala Val Ser  
 20 25 30

Gly Val Glu Gly Leu Pro Pro Gly Ser Ala Leu Leu Val Val Lys Arg  
 35 40 45

Gly Pro Asn Ala Gly Ser Arg Phe Leu Leu Asp Gln Ala Ile Thr Ser  
 50 55 60

Ala Gly Arg His Pro Asp Ser Asp Ile Phe Leu Asp Asp Val Thr Val  
 65 70 75 80

Ser Arg Arg His Ala Glu Phe Arg Leu Glu Asn Asn Glu Phe Asn Val

101

Val Asp Val Gly Ser Leu Asn Gly Thr Tyr Val Asn Arg Glu Pro Val  
 100 105 110

Asp Ser Ala Val Leu Ala Asn Gly Asp Glu Val Gln Ile Gly Lys Leu  
 115 120 125

Arg Leu Val Phe Leu Thr Gly Pro Lys Gln Gly Glu Asp Asp Gly Ser  
 130 135 140

Thr Gly Gly Pro  
 145

## (2) INFORMATION FOR SEQ ID NO:66:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 230 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Thr Ser Asn Arg Pro Ala Arg Arg Gly Arg Arg Ala Pro Arg Asp Thr  
 1 5 10 15

Gly Pro Asp Arg Ser Ala Ser Leu Ser Leu Val Arg His Arg Arg Gln  
 20 25 30

Gln Arg Asp Ala Leu Cys Leu Ser Ser Thr Gln Ile Ser Arg Gln Ser  
 35 40 45

Asn Leu Pro Pro Ala Ala Gly Gly Ala Ala Asn Tyr Ser Arg Arg Asn

102

Phe Asp Val Arg Ile Lys Ile Phe Met Leu Val Thr Ala Val Val Leu  
65 70 75 80

Leu Cys Cys Ser Gly Val Ala Thr Ala Ala Pro Lys Thr Tyr Cys Glu  
85 90 95

Glu Leu Lys Gly Thr Asp Thr Gly Gln Ala Cys Gln Ile Gln Met Ser  
100 105 110

Asp Pro Ala Tyr Asn Ile Asn Ile Ser Leu Pro Ser Tyr Tyr Pro Asp  
115 120 125

Gln Lys Ser Leu Glu Asn Tyr Ile Ala Gln Thr Arg Asp Lys Phe Leu  
130 135 140

Ser Ala Ala Thr Ser Ser Thr Pro Arg Glu Ala Pro Tyr Glu Leu Asn  
145 150 155 160

Ile Thr Ser Ala Thr Tyr Gln Ser Ala Ile Pro Pro Arg Gly Thr Gln  
165 170 175

Ala Val Val Leu Xaa Val Tyr His Asn Ala Gly Gly Thr His Pro Thr  
180 185 190

Thr Thr Tyr Lys Ala Phe Asp Trp Asp Gln Ala Tyr Arg Lys Pro Ile  
195 200 205

Thr Tyr Asp Thr Leu Trp Gln Ala Asp Thr Asp Pro Leu Pro Val Val  
210 215 220

Phe Pro Ile Val Ala Arg  
225 230

(A) LENGTH: 132 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe  
1 5 10 15

Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser  
20 25 30

Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly  
35 40 45

Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val  
50 55 60

Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val  
65 70 75 80

Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala  
85 90 95

Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp  
100 105 110

Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu  
115 120 125

Gly Pro Pro Ala

## (2) INFORMATION FOR SEQ ID NO:68:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 100 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

Val Pro Leu Arg Ser Pro Ser Met Ser Pro Ser Lys Cys Leu Ala Ala  
1 5 10 15

Ala Gln Arg Asn Pro Val Ile Arg Arg Arg Arg Leu Ser Asn Pro Pro  
20 25 30

Pro Arg Lys Tyr Arg Ser Met Pro Ser Pro Ala Thr Ala Ser Ala Gly  
35 40 45

Met Ala Arg Val Arg Arg Arg Ala Ile Trp Arg Gly Pro Ala Thr Xaa  
50 55 60

Ser Ala Gly Met Ala Arg Val Arg Arg Trp Xaa Val Met Pro Xaa Val  
65 70 75 80

Ile Gln Ser Thr Xaa Ile Arg Xaa Xaa Gly Pro Phe Asp Asn Arg Gly  
85 90 95

Ser Glu Arg Lys  
100

## (2) INFORMATION FOR SEQ ID NO:69:

(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Met Thr Asp Asp Ile Leu Leu Ile Asp Thr Asp Glu Arg Val Arg Thr  
1                      5                      10                      15  
Leu Thr Leu Asn Arg Pro Gln Ser Arg Asn Ala Leu Ser Ala Ala Leu  
20                      25                      30  
Arg Asp Arg Phe Phe Ala Xaa Leu Xaa Asp Ala Glu Xaa Asp Asp Asp  
35                      40                      45  
Ile Asp Val Val Ile Leu Thr Gly Ala Asp Pro Val Phe Cys Ala Gly  
50                      55                      60  
Leu Asp Leu Lys Val Ala Gly Arg Ala Asp Arg Ala Ala Gly His Leu  
65                      70                      75                      80  
Thr Ala Val Gly Gly His Asp Gln Ala Gly Asp Arg Arg Asp Gln Arg  
85                      90                      95  
Arg Arg Gly His Arg Arg Ala Arg Thr Gly Ala Val Leu Arg His Pro  
100                      105                      110  
Asp Arg Leu Arg Ala Arg Pro Leu Arg Arg His Pro Arg Pro Gly Gly  
115                      120                      125  
Ala Ala Ala His Leu Gly Thr Gln Cys Val Leu Ala Ala Lys Gly Arg  
130                      135                      140

Asp Arg Arg

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 344 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Met Lys Phe Val Asn His Ile Glu Pro Val Ala Pro Arg Arg Ala Gly  
1                      5                      10                      15

Gly Ala Val Ala Glu Val Tyr Ala Glu Ala Arg Arg Glu Phe Gly Arg  
20                      25                      30

Leu Pro Glu Pro Leu Ala Met Leu Ser Pro Asp Glu Gly Leu Leu Thr  
35                      40                      45

Ala Gly Trp Ala Thr Leu Arg Glu Thr Leu Leu Val Gly Gln Val Pro  
50                      55                      60

Arg Gly Arg Lys Glu Ala Val Ala Ala Ala Val Ala Ala Ser Leu Arg  
65                      70                      75                      80

Cys Pro Trp Cys Val Asp Ala His Thr Thr Met Leu Tyr Ala Ala Gly  
85                      90                      95



Gly Asp Pro Asn Ala Pro Tyr Val Ala Trp Ala Ala Gly Thr Gly Thr  
115 120 125

Pro Ala Gly Pro Pro Ala Pro Phe Gly Pro Asp Val Ala Ala Glu Tyr  
130 135 140

Leu Gly Thr Ala Val Gln Phe His Phe Ile Ala Arg Leu Val Leu Val  
145 150 155 160

Leu Leu Asp Glu Thr Phe Leu Pro Gly Gly Pro Arg Ala Gln Gln Leu  
165 170 175

Met Arg Arg Ala Gly Gly Leu Val Phe Ala Arg Lys Val Arg Ala Glu  
180 185 190

His Arg Pro Gly Arg Ser Thr Arg Arg Leu Glu Pro Arg Thr Leu Pro  
195 200 205

Asp Asp Leu Ala Trp Ala Thr Pro Ser Glu Pro Ile Ala Thr Ala Phe  
210 215 220

Ala Ala Leu Ser His His Leu Asp Thr Ala Pro His Leu Pro Pro Pro  
225 230 235 240

Thr Arg Gln Val Val Arg Arg Val Val Gly Ser Trp His Gly Glu Pro  
245 250 255

Met Pro Met Ser Ser Arg Trp Thr Asn Glu His Thr Ala Glu Leu Pro  
260 265 270

Ala Asp Leu His Ala Pro Thr Arg Leu Ala Leu Leu Thr Gly Leu Ala  
275 280 285

Asp Thr Asp Ala Ala Leu Val Gly Ala Leu Ala Trp Ala Ala Phe Thr  
 305 310 315 320

Ala Ala Arg Arg Ile Gly Thr Trp Ile Gly Ala Ala Ala Glu Gly Gln  
 325 330 335

Val Ser Arg Gln Asn Pro Thr Gly  
 340

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 485 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Asp Asp Pro Asp Met Pro Gly Thr Val Ala Lys Ala Val Ala Asp Ala  
 1 5 10 15

Leu Gly Arg Gly Ile Ala Pro Val Glu Asp Ile Gln Asp Cys Val Glu  
 20 25 30

Ala Arg Leu Gly Glu Ala Gly Leu Asp Asp Val Ala Arg Val Tyr Ile  
 35 40 45

Ile Tyr Arg Gln Arg Arg Ala Glu Leu Arg Thr Ala Lys Ala Leu Leu  
 50 55 60

Gly Val Arg Asp Glu Leu Lys Leu Ser Leu Ala Ala Val Thr Val Leu

109

Arg Glu Arg Tyr Leu Leu His Asp Glu Gln Gly Arg Pro Ala Glu Ser  
85 90 95

Thr Gly Glu Leu Met Asp Arg Ser Ala Arg Cys Val Ala Ala Ala Glu  
100 105 110

Asp Gln Tyr Glu Pro Gly Ser Ser Arg Arg Trp Ala Glu Arg Phe Ala  
115 120 125

Thr Leu Leu Arg Asn Leu Glu Phe Leu Pro Asn Ser Pro Thr Leu Met  
130 135 140

Asn Ser Gly Thr Asp Leu Gly Leu Leu Ala Gly Cys Phe Val Leu Pro  
145 150 155 160

Ile Glu Asp Ser Leu Gln Ser Ile Phe Ala Thr Leu Gly Gln Ala Ala  
165 170 175

Glu Leu G Arg Ala Gly Gly Gly Thr Gly Tyr Ala Phe Ser His Leu  
180 185 190

Arg Pro Ala Gly Asp Arg Val Ala Ser Thr Gly Gly Thr Ala Ser Gly  
195 200 205

Pro Val Ser Phe Leu Arg Leu Tyr Asp Ser Ala Ala Gly Val Val Ser  
210 215 220

Met Gly Gly Arg Arg Arg Gly Ala Cys Met Ala Val Leu Asp Val Ser  
225 230 235 240

His Pro Asp Ile Cys Asp Phe Val Thr Ala Lys Ala Glu Ser Pro Ser  
245 250 255

110

Arg Ala Val Glu Arg Asn Gly Leu His Arg Leu Val Asn Pro Arg Thr  
275 280 285

Gly Lys Ile Val Ala Arg Met Pro Ala Ala Glu Leu Phe Asp Ala Ile  
290 295 300

Cys Lys Ala Ala His Ala Gly Gly Asp Pro Gly Leu Val Phe Leu Asp  
305 310 315 320

Thr Ile Asn Arg Ala Asn Pro Val Pro Gly Arg Gly Arg Ile Glu Ala  
325 330 335

Thr Asn Pro Cys Gly Glu Val Pro Leu Leu Pro Tyr Glu Ser Cys Asn  
340 345 350

Leu Gly Ser Ile Asn Leu Ala Arg Met Leu Ala Asp Gly Arg Val Asp  
355 360 365

Trp Asp Arg Leu Glu Glu Val Ala Gly Val Ala Val Arg Phe Leu Asp  
370 375 380

Asp Val Ile Asp Val Ser Arg Tyr Pro Phe Pro Glu Leu Gly Glu Ala  
385 390 395 400

Ala Arg Ala Thr Arg Lys Ile Gly Leu Gly Val Met Gly Leu Ala Glu  
405 410 415

Leu Leu Ala Ala Leu Gly Ile Pro Tyr Asp Ser Glu Glu Ala Val Arg  
420 425 430

Leu Ala Thr Arg Leu Met Arg Arg Ile Gln Gln Ala Ala His Thr Ala  
435 440 445

Ser Arg Arg Leu Ala Gly Gly Ile Thr Thr Thr Thr

Ser Arg Phe Ala Arg Ser Gly Pro Arg Arg Asn Ala Gln Val Thr Ser  
 465 470 475 480

Val Ala Pro Thr Gly  
 485

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 267 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Gly Val Ile Val Leu Asp Leu Glu Pro Arg Gly Pro Leu Pro Thr Glu  
 1 5 10 15

Ile Tyr Trp Arg Arg Arg Gly Leu Ala Leu Gly Ile Ala Val Val Val  
 20 25 30

Val Gly Ile Ala Val Ala Ile Val Ile Ala Phe Val Asp Ser Ser Ala  
 35 40 45

Gly Ala Lys Pro Val Ser Ala Asp Lys Pro Ala Ser Ala Gln Ser His  
 50 55 60

Pro Gly Ser Pro Ala Pro Gln Ala Pro Gln Pro Ala Gly Gln Thr Glu  
 65 70 75 80

Gly Asn Ala Ala Ala Ala Pro Pro Gln Gly Gln Asn Pro Glu Thr Pro

112

Thr Pro Thr Ala Ala Val Gln Pro Pro Pro Val Leu Lys Glu Gly Asp  
100 105 110

Asp Cys Pro Asp Ser Thr Leu Ala Val Lys Gly Leu Thr Asn Ala Pro  
115 120 125

Gln Tyr Tyr Val Gly Asp Gln Pro Lys Phe Thr Met Val Val Thr Asn  
130 135 140

Ile Gly Leu Val Ser Cys Lys Arg Asp Val Gly Ala Ala Val Leu Ala  
145 150 155 160

Ala Tyr Val Tyr Ser Leu Asp Asn Lys Arg Leu Trp Ser Asn Leu Asp  
165 170 175

Cys Ala Pro Ser Asn Glu Thr Leu Val Lys Thr Phe Ser Pro Gly Glu  
180 185 190

Gln Val Thr Thr Ala Val Thr Trp Thr Gly Met Gly Ser Ala Pro Arg  
195 200 205

Cys Pro Leu Pro Arg Pro Ala Ile Gly Pro Gly Thr Tyr Asn Leu Val  
210 215 220

Val Gln Leu Gly Asn Leu Arg Ser Leu Pro Val Pro Phe Ile Leu Asn  
225 230 235 240

Gln Pro Pro Pro Pro Gly Pro Val Pro Ala Pro Gly Pro Ala Gln  
245 250 255

Ala Pro Pro Pro Glu Ser Pro Ala Gln Gly Gly  
260 265

- (A) LENGTH: 97 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Leu Ile Ser Thr Gly Lys Ala Ser His Ala Ser Leu Gly Val Gln Val  
1                      5                      10                      15  
Thr Asn Asp Lys Asp Thr Pro Gly Ala Lys Ile Val Glu Val Val Ala  
20                      25                      30  
Gly Gly Ala Ala Ala Asn Ala Gly Val Pro Lys Gly Val Val Val Thr  
35                      40                      45  
Lys Val Asp Asp Arg Pro Ile Asn Ser Ala Asp Ala Leu Val Ala Ala  
50                      55                      60  
Val Arg Ser Lys Ala Pro Gly Ala Thr Val Ala Leu Thr Phe Gln Asp  
65                      70                      75                      80  
Pro Ser Gly Gly Ser Arg Thr Val Gln Val Thr Leu Gly Lys Ala Glu  
85                      90                      95  
Gln

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 364 amino acids

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Gly	Ala	Ala	Val	Ser	Leu	Leu	Ala	Ala	Gly	Thr	Leu	Val	Leu	Thr	Ala
1				5					10					15	
Cys	Gly	Gly	Gly	Thr	Asn	Ser	Ser	Ser	Ser	Gly	Ala	Gly	Gly	Thr	Ser
				20					25					30	
Gly	Ser	Val	His	Cys	Gly	Gly	Lys	Lys	Glu	Leu	His	Ser	Ser	Gly	Ser
				35				40						45	
Thr	Ala	Gln	Glu	Asn	Ala	Met	Glu	Gln	Phe	Val	Tyr	Ala	Tyr	Val	Arg
				50				55						60	
Ser	Cys	Pro	Gly	Tyr	Thr	Leu	Asp	Tyr	Asn	Ala	Asn	Gly	Ser	Gly	Ala
				65				70						75	80
Gly	Val	Thr	Gln	Phe	Leu	Asn	Asn	Glu	Thr	Asp	Phe	Ala	Gly	Ser	Asp
				85					90					95	
Val	Pro	Leu	Asn	Pro	Ser	Thr	Gly	Gln	Pro	Asp	Arg	Ser	Ala	Glu	Arg
				100					105					110	
Cys	Gly	Ser	Pro	Ala	Trp	Asp	Leu	Pro	Thr	Val	Phe	Gly	Pro	Ile	Ala
				115					120					125	
Ile	Thr	Tyr	Asn	Ile	Lys	Gly	Val	Ser	Thr	Leu	Asn	Leu	Asp	Gly	Pro
				130					135					140	
Thr	Thr	Ala	Lys	Ile	Phe	Asn	Gly	Thr	Ile	Thr	Val	Trp	Asn	Asp	Pro
				145					150					155	160



Ser Val Ile Phe Arg Ser Asp Lys Ser Gly Thr Ser Asp Asn Phe Gln  
180 185 190

Lys Tyr Leu Asp Gly Val Ser Asn Gly Ala Trp Gly Lys Gly Ala Ser  
195 200 205

Glu Thr Phe Ser Gly Gly Val Gly Val Gly Ala Ser Gly Asn Asn Gly  
210 215 220

Thr Ser Ala Leu Leu Gln Thr Thr Asp Gly Ser Ile Thr Tyr Asn Glu  
225 230 235 240

Trp Ser Phe Ala Val Gly Lys Gln Leu Asn Met Ala Gln Ile Ile Thr  
245 250 255

Ser Ala Gly Pro Asp Pro Val Ala Ile Thr Thr Glu Ser Val Gly Lys  
260 265 270

Thr Ile Ala Gly Ala Lys Ile Met Gly Gln Gly Asn Asp Leu Val Leu  
275 280 285

Asp Thr Ser Ser Phe Tyr Arg Pro Thr Gln Pro Gly Ser Tyr Pro Ile  
290 295 300

Val Leu Ala Thr Tyr Glu Ile Val Cys Ser Lys Tyr Pro Asp Ala Thr  
305 310 315 320

Thr Gly Thr Ala Val Arg Ala Phe Met Gln Ala Ala Ile Gly Pro Gly  
325 330 335

Gln Glu Gly Leu Asp Gln Tyr Gly Ser Ile Pro Leu Pro Lys Ser Phe  
340 345 350

## (2) INFORMATION FOR SEQ ID NO:75:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 309 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Gln Ala Ala Ala Gly Arg Ala Val Arg Arg Thr Gly His Ala Glu Asp  
1                   5                   10                   15

Gln Thr His Gln Asp Arg Leu His His Gly Cys Arg Arg Ala Ala Val  
20                   25                   30

Val Val Arg Gln Asp Arg Ala Ser Val Ser Ala Thr Ser Ala Arg Pro  
35                   40                   45

Pro Arg Arg His Pro Ala Gln Gly His Arg Arg Arg Val Ala Pro Ser  
50                   55                   60

Gly Gly Arg Arg Arg Pro His Pro His His Val Gln Pro Asp Asp Arg  
65                   70                   75                   80

Arg Asp Arg Pro Ala Leu Leu Asp Arg Thr Gln Pro Ala Glu His Pro  
85                   90                   95

Asp Pro His Arg Arg Gly Pro Ala Asp Pro Gly Arg Val Arg Gly Arg  
100                   105                   110

Ala Asp His Gly Ala Pro Val Arg Gly Arg Gly Pro His Arg Gly Val  
130 135 140

Gln His Arg Gly Gly Pro Val Phe Val Arg Arg Val Pro Gly Val Arg  
145 150 155 160

Cys Ala His Arg Arg Gly His Arg Arg Val Ala Ala Pro Gly Gln Gly  
165 170 175

Asp Val Leu Arg Ala Gly Leu Arg Val Glu Arg Leu Arg Pro Val Ala  
180 185 190

Ala Val Glu Asn Leu His Arg Gly Ser Gln Arg Ala Asp Gly Arg Val  
195 200 205

Phe Arg Pro Ile Arg Arg Gly Ala Arg Leu Pro Ala Arg Arg Ser Arg  
210 215 220

Ala Gly Pro Gln Gly Arg Leu His Leu Asp Gly Ala Gly Pro Ser Pro  
225 230 235 240

Leu Pro Ala Arg Ala Gly Gln Gln Gln Pro Ser Ser Ala Gly Gly Arg  
245 250 255

Arg Ala Gly Gly Ala Glu Arg Ala Asp Pro Gly Gln Arg Gly Arg His  
260 265 270

His Gln Gly Gly His Asp Pro Gly Arg Gln Gly Ala Gln Arg Gly Thr  
275 280 285

Ala Gly Val Ala His Ala Ala Ala Gly Pro Arg Arg Ala Ala Val Arg  
290 295 300

## (2) INFORMATION FOR SEQ ID NO:76:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 580 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

Ser Ala Val Trp Cys Leu Asn Gly Phe Thr Gly Arg His Arg His Gly  
 1 5 10 15

Arg Cys Arg Val Arg Ala Ser Gly Trp Arg Ser Ser Asn Arg Trp Cys  
 20 25 30

Ser Thr Thr Ala Asp Cys Cys Ala Ser Lys Thr Pro Thr Gln Ala Ala  
 35 40 45

Ser Pro Leu Glu Arg Arg Phe Thr Cys Cys Ser Pro Ala Val Gly Cys  
 50 55 60

Arg Phe Arg Ser Phe Pro Val Arg Arg Leu Ala Leu Gly Ala Arg Thr  
 65 70 75 80

Ser Arg Thr Leu Gly Val Arg Arg Thr Leu Ser Gln Trp Asn Leu Ser  
 85 90 95

Pro Arg Ala Gln Pro Ser Cys Ala Val Thr Val Glu Ser His Thr His  
 100 105 110

Ala Ser Pro Arg Met Ala Lys Leu Ala Arg Val Val Gly Leu Val Gln

Glu Glu Gln Pro Ser Asp Met Thr Asn His Pro Arg Tyr Ser Pro Pro  
130 135 140

Pro Gln Gln Pro Gly Thr Pro Gly Tyr Ala Gln Gly Gln Gln Gln Thr  
145 150 155 160

Tyr Ser Gln Gln Phe Asp Trp Arg Tyr Pro Pro Ser Pro Pro Gln  
165 170 175

Pro Thr Gln Tyr Arg Gln Pro Tyr Glu Ala Leu Gly Gly Thr Arg Pro  
180 185 190

Gly Leu Ile Pro Gly Val Ile Pro Thr Met Thr Pro Pro Gly Met  
195 200 205

Val Arg Gln Arg Pro Arg Ala Gly Met Leu Ala Ile Gly Ala Val Thr  
210 215 220

Ile Ala Val Val Ser Ala Gly Ile Gly Gly Ala Ala Ala Ser Leu Val  
225 230 235 240

Gly Phe Asn Arg Ala Pro Ala Gly Pro Ser Gly Gly Pro Val Ala Ala  
245 250 255

Ser Ala Ala Pro Ser Ile Pro Ala Ala Asn Met Pro Pro Gly Ser Val  
260 265 270

Glu Gln Val Ala Ala Lys Val Val Pro Ser Val Val Met Leu Glu Thr  
275 280 285

Asp Leu Gly Arg Gln Ser Glu Glu Gly Ser Gly Ile Ile Leu Ser Ala  
290 295 300

Pro Pro Leu Gly Ser Pro Pro Pro Lys Thr Thr Val Thr Phe Ser Asp  
325 330 335

Gly Arg Thr Ala Pro Phe Thr Val Val Gly Ala Asp Pro Thr Ser Asp  
340 345 350

Ile Ala Val Val Arg Val Gln Gly Val Ser Gly Leu Thr Pro Ile Ser  
355 360 365

Leu Gly Ser Ser Ser Asp Leu Arg Val Gly Gln Pro Val Leu Ala Ile  
370 375 380

Gly Ser Pro Leu Gly Leu Glu Gly Thr Val Thr Thr Gly Ile Val Ser  
385 390 395 400

Ala Leu Asn Arg Pro Val Ser Thr Thr Gly Glu Ala Gly Asn Gln Asn  
405 410 415

Thr Val Leu Asp Ala Ile Gln Thr Asp Ala Ala Ile Asn Pro Gly Asn  
420 425 430

Ser Gly Gly Ala Leu Val Asn Met Asn Ala Gln Leu Val Gly Val Asn  
435 440 445

Ser Ala Ile Ala Thr Leu Gly Ala Asp Ser Ala Asp Ala Gln Ser Gly  
450 455 460

Ser Ile Gly Leu Gly Phe Ala Ile Pro Val Asp Gln Ala Lys Arg Ile  
465 470 475 480

Ala Asp Glu Leu Ile Ser Thr Gly Lys Ala Ser His Ala Ser Leu Gly  
485 490 495

121

Val Val Ala Gly Gly Ala Ala Asn Ala Gly Val Pro Lys Gly Val  
 515 520 525

Val Val Thr Lys Val Asp Asp Arg Pro Ile Asn Ser Ala Asp Ala Leu  
 530 535 540

Val Ala Ala Val Arg Ser Lys Ala Pro Gly Ala Thr Val Ala Leu Thr  
 545 550 555 560

Phe Gln Asp Pro Ser Gly Gly Ser Arg Thr Val Gln Val Thr Leu Gly  
 565 570 575

Lys Ala Glu Gln  
 580

## (2) INFORMATION FOR SEQ ID NO:77:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 233 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Met Asn Asp Gly Lys Arg Ala Val Thr Ser Ala Val Leu Val Val Leu  
 1 5 10 15

Gly Ala Cys Leu Ala Leu Trp Leu Ser Gly Cys Ser Ser Pro Lys Pro  
 20 25 30

Asp Ala Glu Glu Gln Gly Val Pro Val Ser Pro Thr Ala Ser Asp Pro

Ala Leu Leu Ala Glu Ile Arg Gln Ser Leu Asp Ala Thr Lys Gly Leu  
50 55 60

Thr Ser Val His Val Ala Val Arg Thr Thr Gly Lys Val Asp Ser Leu  
65 70 75 80

Leu Gly Ile Thr Ser Ala Asp Val Asp Val Arg Ala Asn Pro Leu Ala  
85 90 95

Ala Lys Gly Val Cys Thr Tyr Asn Asp Glu Gln Gly Val Pro Phe Arg  
100 105 110

Val Gln Gly Asp Asn Ile Ser Val Lys Leu Phe Asp Asp Trp Ser Asn  
115 120 125

Leu Gly Ser Ile Ser Glu Leu Ser Thr Ser Arg Val Leu Asp Pro Ala  
130 135 140

Ala Gly Val Thr Gln Leu Leu Ser Gly Val Thr Asn Leu Gln Ala Gln  
145 150 155 160

Gly Thr Glu Val Ile Asp Gly Ile Ser Thr Thr Lys Ile Thr Gly Thr  
165 170 175

Ile Pro Ala Ser Ser Val Lys Met Leu Asp Pro Gly Ala Lys Ser Ala  
180 185 190

Arg Pro Ala Thr Val Trp Ile Ala Gln Asp Gly Ser His His Leu Val  
195 200 205

Arg Ala Ser Ile Asp Leu Gly Ser Gly Ser Ile Gln Leu Thr Gln Ser  
210 215 220



## (2) INFORMATION FOR SEQ ID NO:78:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 66 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Val Ile Asp Ile Ile Gly Thr Ser Pro Thr Ser Trp Glu Gln Ala Ala  
1                      5                      10                      15

Ala Glu Ala Val Gln Arg Ala Arg Asp Ser Val Asp Asp Ile Arg Val  
20                      25                      30

Ala Arg Val Ile Glu Gln Asp Met Ala Val Asp Ser Ala Gly Lys Ile  
35                      40                      45

Thr Tyr Arg Ile Lys Leu Glu Val Ser Phe Lys Met Arg Pro Ala Gln  
50                      55                      60

Pro Arg  
65

## (2) INFORMATION FOR SEQ ID NO:79:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 69 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Val Pro Pro Ala Pro Pro Leu Pro Pro Leu Pro Pro Ser Pro Ile Ser  
 1                      5                      10                      15

Cys Ala Ser Pro Pro Ser Pro Pro Leu Pro Pro Ala Pro Pro Val Ala  
                     20                      25                      30

Pro Gly Pro Pro Met Pro Pro Leu Asp Pro Trp Pro Pro Ala Pro Pro  
                     35                      40                      45

Leu Pro Tyr Ser Thr Pro Pro Gly Ala Pro Leu Pro Pro Ser Pro Pro  
                     50                      55                      60

Ser Pro Pro Leu Pro  
 65

## (2) INFORMATION FOR SEQ ID NO:80:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 355 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

Met Ser Asn Ser Arg Arg Arg Ser Leu Arg Trp Ser Trp Leu Leu Ser  
 1                      5                      10                      15

Val Leu Ala Ala Val Gly Leu Gly Leu Ala Thr Ala Pro Ala Gln Ala  
                     20                      25                      30

125

Pro Leu Asp Pro Ser Ala Met Val Ala Gln Val Ala Pro Gln Val Val  
50 55 60

Asn Ile Asn Thr Lys Leu Gly Tyr Asn Asn Ala Val Gly Ala Gly Thr  
65 70 75 80

Gly Ile Val Ile Asp Pro Asn Gly Val Val Leu Thr Asn Asn His Val  
85 90 95

Ile Ala Gly Ala Thr Asp Ile Asn Ala Phe Ser Val Gly Ser Gly Gln  
100 105 110

Thr Tyr Gly Val Asp Val Val Gly Tyr Asp Arg Thr Gln Asp Val Ala  
115 120 125

Val Leu Gln Leu Arg Gly Ala Gly Gly Leu Pro Ser Ala Ala Ile Gly  
130 135 140

Gly Gly Val Ala Val Gly Glu Pro Val Val Ala Met Gly Asn Ser Gly  
145 150 155 160

Gly Gln Gly Gly Thr Pro Arg Ala Val Pro Gly Arg Val Val Ala Leu  
165 170 175

Gly Gln Thr Val Gln Ala Ser Asp Ser Leu Thr Gly Ala Glu Glu Thr  
180 185 190

Leu Asn Gly Leu Ile Gln Phe Asp Ala Ala Ile Gln Pro Gly Asp Ser  
195 200 205

Gly Gly Pro Val Val Asn Gly Leu Gly Gln Val Val Gly Met Asn Thr  
210 215 220

Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser Gly  
245 250 255

Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly Leu  
260 265 270

Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val Val  
275 280 285

Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val Ile  
290 295 300

Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala Asp  
305 310 315 320

Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp Gln  
325 330 335

Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu Gly  
340 345 350

Pro Pro Ala  
355

(2) INFORMATION FOR SEQ ID NO:81:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 205 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

127

Ser Pro Lys Pro Asp Ala Glu Glu Gln Gly Val Pro Val Ser Pro Thr  
1 5 10 15

Ala Ser<sup>-</sup> Asp Pro Ala Leu Leu Ala Glu Ile Arg Gln Ser Leu Asp Ala  
20 25 30

Thr Lys Gly Leu Thr Ser Val His Val Ala Val Arg Thr Thr Gly Lys  
35 40 45

Val Asp Ser Leu Leu Gly Ile Thr Ser Ala Asp Val Asp Val Arg Ala  
50 55 60

Asn Pro Leu Ala Ala Lys Gly Val Cys Thr Tyr Asn Asp Glu Gln Gly  
65 70 75 80

Val Pro Phe Arg Val Gln Gly Asp Asn Ile Ser Val Lys Leu Phe Asp  
85 90 95

Asp Trp Ser Asn Leu Gly Ser Ile Ser Glu Leu Ser Thr Ser Arg Val  
100 105 110

Leu Asp Pro Ala Ala Gly Val Thr Gln Leu Leu Ser Gly Val Thr Asn  
115 120 125

Leu Gln Ala Gln Gly Thr Glu Val Ile Asp Gly Ile Ser Thr Thr Lys  
130 135 140

Ile Thr Gly Thr Ile Pro Ala Ser Ser Val Lys Met Leu Asp Pro Gly  
145 150 155 160

Ala Lys Ser Ala Arg Pro Ala Thr Val Trp Ile Ala Gln Asp Gly Ser  
165 170 175

Leu Thr Gln Ser Lys Trp Asn Glu Pro Val Asn Val Asp  
 195 200 205

## (2) INFORMATION FOR SEQ ID NO:82:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 286 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

Gly Asp Ser Phe Trp Ala Ala Ala Asp Gln Met Ala Arg Gly Phe Val  
 1 5 10 15

Leu Gly Ala Thr Ala Gly Arg Thr Thr Leu Thr Gly Glu Gly Leu Gln  
 20 25 30

His Ala Asp Gly His Ser Leu Leu Leu Asp Ala Thr Asn Pro Ala Val  
 35 40 45

Val Ala Tyr Asp Pro Ala Phe Ala Tyr Glu Ile Gly Tyr Ile Xaa Glu  
 50 55 60

Ser Gly Leu Ala Arg Met Cys Gly Glu Asn Pro Glu Asn Ile Phe Phe  
 65 70 75 80

Tyr Ile Thr Val Tyr Asn Glu Pro Tyr Val Gln Pro Pro Glu Pro Glu  
 85 90 95

Asn Phe Asp Pro Glu Gly Val Leu Gly Gly Ile Tyr Arg Tyr His Ala

129

Ala Thr Glu Gln Arg Thr Asn Lys Xaa Gln Ile Leu Ala Ser Gly Val  
115 120 125

Ala Met Pro Ala Ala Leu Arg Ala Ala Gln Met Leu Ala Ala Glu Trp  
130 135 140

Asp Val Ala Ala Asp Val Trp Ser Val Thr Ser Trp Gly Glu Leu Asn  
145 150 155 160

Arg Asp Gly Val Val Ile Glu Thr Glu Lys Leu Arg His Pro Asp Arg  
165 170 175

Pro Ala Gly Val Pro Tyr Val Thr Arg Ala Leu Glu Asn Ala Arg Gly  
180 185 190

Pro Val Ile Ala Val Ser Asp Trp Met Arg Ala Val Pro Glu Gln Ile  
195 200 205

Arg Pro Trp Val Pro Gly Thr Tyr Leu Thr Leu Gly Thr Asp Gly Phe  
210 215 220

Gly Phe Ser Asp Thr Arg Pro Ala Gly Arg Arg Tyr Phe Asn Thr Asp  
225 230 235 240

Ala Glu Ser Gln Val Gly Arg Gly Phe Gly Arg Gly Trp Pro Gly Arg  
245 250 255

Arg Val Asn Ile Asp Pro Phe Gly Ala Gly Arg Gly Pro Pro Ala Gln  
260 265 270

Leu Pro Gly Phe Asp Glu Gly Gly Gly Leu Arg Pro Xaa Lys  
275 280 285

(A) LENGTH: 173 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

Thr	Lys	Phe	His	Ala	Leu	Met	Gln	Glu	Gln	Ile	His	Asn	Glu	Phe	Thr
1				5						10				15	
Ala	Ala	Gln	Gln	Tyr	Val	Ala	Ile	Ala	Val	Tyr	Phe	Asp	Ser	Glu	Asp
			20					25						30	
Leu	Pro	Gln	Leu	Ala	Lys	His	Phe	Tyr	Ser	Gln	Ala	Val	Glu	Glu	Arg
			35				40							45	
Asn	His	Ala	Met	Met	Leu	Val	Gln	His	Leu	Leu	Asp	Arg	Asp	Leu	Arg
			50				55							60	
Val	Glu	Ile	Pro	Gly	Val	Asp	Thr	Val	Arg	Asn	Gln	Phe	Asp	Arg	Pro
65					70					75				80	
Arg	Glu	Ala	Leu	Ala	Leu	Ala	Leu	Asp	Gln	Glu	Arg	Thr	Val	Thr	Asp
			85						90					95	
Gln	Val	Gly	Arg	Leu	Thr	Ala	Val	Ala	Arg	Asp	Glu	Gly	Asp	Phe	Leu
			100						105					110	
Gly	Glu	Gln	Phe	Met	Gln	Trp	Phe	Leu	Gln	Glu	Gln	Ile	Glu	Glu	Val
			115					120						125	
Ala	Leu	Met	Ala	Thr	Leu	Val	Arg	Val	Ala	Asp	Arg	Ala	Gly	Ala	Asn



Leu Phe Glu Leu Glu Asn Phe Val Ala Arg Glu Val Asp Val Ala Pro  
 145 150 155 160

Ala Ala Ser Gly Ala Pro His Ala Ala Gly Gly Arg Leu  
 165 170

## (2) INFORMATION FOR SEQ ID NO:84:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 107 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

Arg Ala Asp Glu Arg Lys Asn Thr Thr Met Lys Met Val Lys Ser Ile  
 1 5 10 15

Ala Ala Gly Leu Thr Ala Ala Ala Ala Ile Gly Ala Ala Ala Gly  
 20 25 30

Val Thr Ser Ile Met Ala Gly Gly Pro Val Val Tyr Gln Met Gln Pro  
 35 40 45

Val Val Phe Gly Ala Pro Leu Pro Leu Asp Pro Xaa Ser Ala Pro Xaa  
 50 55 60

Val Pro Thr Ala Ala Gln Trp Thr Xaa Leu Leu Asn Xaa Leu Xaa Asp  
 65 70 75 80

Pro Asn Val Ser Phe Xaa Asn Lys Gly Ser Leu Val Gly Gly Gly Gly

132

Gly Gly Xaa Glu Gly Xaa Xaa Arg Arg Xaa Gln  
 100 105

## (2) INFORMATION FOR SEQ ID NO:85:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 125 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Val Leu Ser Val Pro Val Gly Asp Gly Phe Trp Xaa Arg Val Val Asn  
 1 5 10 15

Pro Leu Gly Gln Pro Ile Asp Gly Arg Gly Asp Val Asp Ser Asp Thr  
 20 25 30

Arg Arg Ala Leu Glu Leu Gln Ala Pro Ser Val Val Xaa Arg Gln Gly  
 35 40 45

Val Lys Glu Pro Leu Xaa Thr Gly Ile Lys Ala Ile Asp Ala Met Thr  
 50 55 60

Pro Ile Gly Arg Gly Gln Arg Gln Leu Ile Ile Gly Asp Arg Lys Thr  
 65 70 75 80

Gly Lys Asn Arg Arg Leu Cys Arg Thr Pro Ser Ser Asn Gln Arg Glu  
 85 90 95

Glu Leu Gly Val Arg Trp Ile Pro Arg Ser Arg Cys Ala Cys Val Tyr  
 100 105 110

## (2) INFORMATION FOR SEQ ID NO:86:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 117 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

Cys Asp Ala Val Met Gly Phe Leu Gly Gly Ala Gly Pro Leu Ala Val  
1 5 10 15

Val Asp Gln Gln Leu Val Thr Arg Val Pro Gln Gly Trp Ser Phe Ala  
20 25 30

Gln Ala Ala Ala Val Pro Val Val Phe Leu Thr Ala Trp Tyr Gly Leu  
35 40 45

Ala Asp Leu Ala Glu Ile Lys Ala Gly Glu Ser Val Leu Ile His Ala  
50 55 60

Gly Thr Gly Gly Val Gly Met Ala Ala Val Gln Leu Ala Arg Gln Trp  
65 70 75 80

Gly Val Glu Val Phe Val Thr Ala Ser Arg Gly Lys Trp Asp Thr Leu  
85 90 95

Arg Ala Xaa Xaa Phe Asp Asp Xaa Pro Tyr Arg Xaa Phe Pro His Xaa  
100 105 110

## (2) INFORMATION FOR SEQ ID NO:87:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 103 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

Met Tyr Arg Phe Ala Cys Arg Thr Leu Met Leu Ala Ala Cys Ile Leu  
1 5 10 15

Ala Thr Gly Val Ala Gly Leu Gly Val Gly Ala Gln Ser Ala Ala Gln  
20 25 30

Thr Ala Pro Val Pro Asp Tyr Tyr Trp Cys Pro Gly Gln Pro Phe Asp  
35 40 45

Pro Ala Trp Gly Pro Asn Trp Asp Pro Tyr Thr Cys His Asp Asp Phe  
50 55 60

His Arg Asp Ser Asp Gly Pro Asp His Ser Arg Asp Tyr Pro Gly Pro  
65 70 75 80

Ile Leu Glu Gly Pro Val Leu Asp Asp Pro Gly Ala Ala Pro Pro Pro  
85 90 95

Pro Ala Ala Gly Gly Gly Ala  
100

## (2) INFORMATION FOR SEQ ID NO:88:

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

Val Gln Cys Arg Val Trp Leu Glu Ile Gln Trp Arg Gly Met Leu Gly  
1 5 10 15  
Ala Asp Gln Ala Arg Ala Gly Gly Pro Ala Arg Ile Trp Arg Glu His  
20 25 30  
Ser Met Ala Ala Met Lys Pro Arg Thr Gly Asp Gly Pro Leu Glu Ala  
35 40 45  
Thr Lys Glu Gly Arg Gly Ile Val Met Arg Val Pro Leu Glu Gly Gly  
50 55 60  
Gly Arg Leu Val Val Glu Leu Thr Pro Asp Glu Ala Ala Ala Leu Gly  
65 70 75 80  
Asp Glu Leu Lys Gly Val Thr Ser  
85

(2) INFORMATION FOR SEQ ID NO:89:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 95 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

Thr Asp Ala Ala Thr Leu Ala Gln Glu Ala Gly Asn Phe Glu Arg Ile  
1 5 10 15

Ser Gly Asp Leu Lys Thr Gln Ile Asp Gln Val Glu Ser Thr Ala Gly  
20 25 30

Ser Leu Gln Gly Gln Trp Arg Gly Ala Ala Gly Thr Ala Ala Gln Ala  
35 40 45

Ala Val Val Arg Phe Gln Glu Ala Ala Asn Lys Gln Lys Gln Glu Leu  
50 55 60

Asp Glu Ile Ser Thr Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser Arg  
65 70 75 80

Ala Asp Glu Glu Gln Gln Gln Ala Leu Ser Ser Gln Met Gly Phe  
85 90 95

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 166 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Met Thr Gln Ser Gln Thr Val Thr Val Asp Gln Gln Glu Ile Leu Asn  
1 5 10 15

Arg Ala Asn Glu Val Glu Ala Pro Met Ala Asp Pro Pro Thr Asp Val

137

Pro Ile Thr Pro Cys Glu Leu Thr Xaa Xaa Lys Asn Ala Ala Gln Gln  
 35 40 45

Xaa Val Leu Ser Ala Asp Asn Met Arg Glu Tyr Leu Ala Ala Gly Ala  
 50 55 60

Lys Glu Arg Gln Arg Leu Ala Thr Ser Leu Arg Asn Ala Ala Lys Xaa  
 65 70 75 80

Tyr Gly Glu Val Asp Glu Glu Ala Ala Thr Ala Leu Asp Asn Asp Gly  
 85 90 95

Glu Gly Thr Val Gln Ala Glu Ser Ala Gly Ala Val Gly Gly Asp Ser  
 100 105 110

Ser Ala Glu Leu Thr Asp Thr Pro Arg Val Ala Thr Ala Gly Glu Pro  
 115 120 125

Asn Phe Met Asp Leu Lys Glu Ala Ala Arg Lys Leu Glu Thr Gly Asp  
 130 135 140

Gln Gly Ala Ser Leu Ala His Xaa Gly Asp Gly Trp Asn Thr Xaa Thr  
 145 150 155 160

Leu Thr Leu Gln Gly Asp  
 165

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Arg Ala Glu Arg Met  
1                      5

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 263 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

Val Ala Trp Met Ser Val Thr Ala Gly Gln Ala Glu Leu Thr Ala Ala  
1                      5                      10                      15

Gln Val Arg Val Ala Ala Ala Tyr Glu Thr Ala Tyr Gly Leu Thr  
20                      25                      30

Val Pro Pro Pro Val Ile Ala Glu Asn Arg Ala Glu Leu Met Ile Leu  
35                      40                      45

Ile Ala Thr Asn Leu Leu Gly Gln Asn Thr Pro Ala Ile Ala Val Asn  
50                      55                      60

Glu Ala Glu Tyr Gly Glu Met Trp Ala Gln Asp Ala Ala Ala Met Phe  
65                      70                      75                      80

Gly Tyr Ala Ala Ala Thr Ala Thr Ala Thr Ala Thr Leu Leu Pro Phe  
85                      90                      95



139

Ala Ala Val Glu Glu Ala Ser Asp Thr Ala Ala Ala Asn Gln Leu Met  
115 120 125

Asn Asn Val Pro Gln Ala Leu Lys Gln Leu Ala Gln Pro Thr Gln Gly  
130 135 140

Thr Thr Pro Ser Ser Lys Leu Gly Gly Leu Trp Lys Thr Val Ser Pro  
145 150 155 160

His Arg. Ser Pro Ile Ser Asn Met Val Ser Met Ala Asn Asn His Met.  
165 170 175

Ser Met Thr Asn Ser Gly Val Ser Met Thr Asn Thr Leu Ser Ser Met  
180 185 190

Leu Lys Gly Phe Ala Pro Ala Ala Ala Gln Ala Val Gln Thr Ala  
195 200 205

Ala Gln Asn Gly Val Arg Ala Met Ser Ser Leu Gly Ser Ser Leu Gly  
210 215 220

Ser Ser Gly Leu Gly Gly Gly Val Ala Ala Asn Leu Gly Arg Ala Ala  
225 230 235 240

Ser Val Arg Tyr Gly His Arg Asp Gly Gly Lys Tyr Ala Xaa Ser Gly  
245 250 255

Arg Arg Asn Gly Gly Pro Ala  
260

(2) INFORMATION FOR SEQ ID NO:93:

(A) SEQUENCE CHARACTERISTICS:

140

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

Met Thr Tyr Ser Pro Gly Asn Pro Gly Tyr Pro Gln Ala Gln Pro Ala  
1 5 10 15

Gly Ser Tyr Gly Gly Val Thr Pro Ser Phe Ala His Ala Asp Glu Gly  
20 25 30

Ala Ser Lys Leu Pro Met Tyr Leu Asn Ile Ala Val Ala Val Leu Gly  
35 40 45

Leu Ala Ala Tyr Phe Ala Ser Phe Gly Pro Met Phe Thr Leu Ser Thr  
50 55 60

Glu Leu Gly Gly Gly Asp Gly Ala Val Ser Gly Asp Thr Gly Leu Pro  
65 70 75 80

Val Gly Val Ala Leu Leu Ala Ala Leu Leu Ala Gly Val Val Leu Val  
85 90 95

Pro Lys Ala Lys Ser His Val Thr Val Val Ala Val Leu Gly Val Leu  
100 105 110

Gly Val Phe Leu Met Val Ser Ala Thr Phe Asn Lys Pro Ser Ala Tyr  
115 120 125

Ser Thr Gly Trp Ala Leu Trp Val Val Leu Ala Phe Ile Val Phe Gln  
130 135 140

141

Ala Pro Ala Pro Arg Pro Lys Phe Asp Pro Tyr Gly Gln Tyr Gly Arg  
 165 170 175

Tyr Gly Gln Tyr Gly Gln Tyr Gly Val Gln Pro Gly Gly Tyr Tyr Gly  
 180 185 190

Gln Gln Gly Ala Gln Gln Ala Ala Gly Leu Gln Ser Pro Gly Pro Gln  
 195 200 205

Gln Ser Pro Gln Pro Pro Gly Tyr Gly Ser Gln Tyr Gly Gly Tyr Ser  
 210 215 220

Ser Ser Pro Ser Gln Ser Gly Ser Gly Tyr Thr Ala Gln Pro Pro Ala  
 225 230 235 240

Gln Pro Pro Ala Gln Ser Gly Ser Gln Gln Ser His Gln Gly Pro Ser  
 245 250 255

Thr Pro Pro Thr Gly Phe Pro Ser Phe Ser Pro Pro Pro Val Ser  
 260 265 270

Ala Gly Thr Gly Ser Gln Ala Gly Ser Ala Pro Val Asn Tyr Ser Asn  
 275 280 285

Pro Ser Gly Gly Glu Gln Ser Ser Ser Pro Gly Gly Ala Pro Val  
 290 295 300

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 168 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

Met	Lys	Met	Val	Lys	Ser	Ile	Ala	Ala	Gly	Leu	Thr	Ala	Ala	Ala	Ala
1				5					10					15	
Ile	Gly	Ala	Ala	Ala	Ala	Gly	Val	Thr	Ser	Ile	Met	Ala	Gly	Gly	Pro
				20				25						30	
Val	Val	Tyr	Gln	Met	Gln	Pro	Val	Val	Phe	Gly	Ala	Pro	Leu	Pro	Leu
				35			40						45		
Asp	Pro	Ala	Ser	Ala	Pro	Asp	Val	Pro	Thr	Ala	Ala	Gln	Leu	Thr	Ser
				50			55						60		
Leu	Leu	Asn	Ser	Leu	Ala	Asp	Pro	Asn	Val	Ser	Phe	Ala	Asn	Lys	Gly
65					70					75				80	
Ser	Leu	Val	Glu	Gly	Gly	Ile	Gly	Gly	Thr	Glu	Ala	Arg	Ile	Ala	Asp
				85					90					95	
His	Lys	Leu	Lys	Lys	Ala	Ala	Glu	His	Gly	Asp	Leu	Pro	Leu	Ser	Phe
				100					105					110	
Ser	Val	Thr	Asn	Ile	Gln	Pro	Ala	Ala	Ala	Gly	Ser	Ala	Thr	Ala	Asp
				115					120					125	
Val	Ser	Val	Ser	Gly	Pro	Lys	Leu	Ser	Ser	Pro	Val	Thr	Gln	Asn	Val
				130			135						140		
Thr	Phe	Val	Asn	Gln	Gly	Gly	Trp	Met	Leu	Ser	Arg	Ala	Ser	Ala	Met
145					150					155				160	
Glu	Leu	Leu	Gln	Ala	Ala	Gly	Asn								

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 332 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

Met His His His His His Met His Gln Val Asp Pro Asn Leu Thr  
1 5 10 15

Arg Arg Lys Gly Arg Leu Ala Ala Leu Ala Ile Ala Ala Met Ala Ser  
20 25 30

Ala Ser Leu Val Thr Val Ala Val Pro Ala Thr Ala Asn Ala Asp Pro  
35 40 45

Glu Pro Ala Pro Pro Val Pro Thr Thr Ala Ala Ser Pro Pro Ser Thr  
50 55 60

Ala Ala Ala Pro Pro Ala Pro Ala Thr Pro Val Ala Pro Pro Pro Pro  
65 70 75 80

Ala Ala Ala Asn Thr Pro Asn Ala Gln Pro Gly Asp Pro Asn Ala Ala  
85 90 95

Pro Pro Pro Ala Asp Pro Asn Ala Pro Pro Pro Pro Val Ile Ala Pro  
100 105 110

Asn Ala Pro Gln Pro Val Arg Ile Asp Asn Pro Val Gly Gly Phe Ser  
115 120 125

Tyr Gly Ser Ala Leu Leu Ser Lys Thr Thr Gly Asp Pro Pro Phe Pro  
145 150 155 160

Gly Gln Pro Pro Pro Val Ala Asn Asp Thr Arg Ile Val Leu Gly Arg  
165 170 175

Leu Asp Gln Lys Leu Tyr Ala Ser Ala Glu Ala Thr Asp Ser Lys Ala  
180 185 190

Ala Ala Arg Leu Gly Ser Asp Met Gly Glu Phe Tyr Met Pro Tyr Pro  
195 200 205

Gly Thr Arg Ile Asn Gln Glu Thr Val Ser Leu Asp Ala Asn Gly Val  
210 215 220

Ser Gly Ser Ala Ser Tyr Tyr Glu Val Lys Phe Ser Asp Pro Ser Lys  
225 230 235 240

Pro Asn Gly Gln Ile Trp Thr Gly Val Ile Gly Ser Pro Ala Ala Asn  
245 250 255

Ala Pro Asp Ala Gly Pro Pro Gln Arg Trp Phe Val Val Trp Leu Gly  
260 265 270

Thr Ala Asn Asn Pro Val Asp Lys Gly Ala Ala Lys Ala Leu Ala Glu  
275 280 285

Ser Ile Arg Pro Leu Val Ala Pro Pro Pro Ala Pro Ala Pro Ala Pro  
290 295 300

Ala Glu Pro Ala Pro Ala Pro Ala Pro Ala Gly Glu Val Ala Pro Thr  
305 310 315 320

## (2) INFORMATION FOR SEQ ID NO:96:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 500 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

CGTGGCAATG TCGTTGACCG TCGGGGCCGG GGTGCCTCC GCAGATCCCG TGGACGCGGT	60
CATTAACACC ACCTGCAATT ACGGGCAGGT AGTAGCTGCG CTCAACGCGA CGGATCCGGG	120
GGCTGCCGCA CAGTTCAACG CCTCACCGGT GGCAGCTCC TATTGCGCA ATTCCTCGC	180
CGCACCGCCA CCTCAGCGCG CTGCCATGGC CGCGCAATTG CAAGCTGTGC CGGGGGCGGC	240
ACAGTACATC GGCCTTGTGC AGTCGGTTGC CGGCTCCTGC AACAACTATT AAGCCCATGC	300
GGGCCCCATC CCGCGACCCG GCATCGTCGC CGGGGCTAGG CCAGATTGCC CCGCTCCTCA	360
ACGGGCGGCA TCCCGCGACC CGGCATCGTC GCCGGGGCTA GGCCAGATTG CCCCCTCCT	420
CAACGGGCGG CATCTCGTGC CGAATTCCTG CAGCCCGGGG GATCCACTAG TTCTAGAGCG	480
GCCGCCACCG CGGTGGAGCT	500

## (2) INFORMATION FOR SEQ ID NO:97:

## (i) SEQUENCE CHARACTERISTICS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

Val Ala Met Ser Leu Thr Val Gly Ala Gly Val Ala Ser Ala Asp Pro  
1                      5                      10                      15

Val Asp Ala Val Ile Asn Thr Thr Cys Asn Tyr Gly Gln Val Val Ala  
20                      25                      30

Ala Leu Asn Ala Thr Asp Pro Gly Ala Ala Ala Gln Phe Asn Ala Ser  
35                      40                      45

Pro Val Ala Gln Ser Tyr Leu Arg Asn Phe Leu Ala Ala Pro Pro Pro  
50                      55                      60

Gln Arg Ala Ala Met Ala Ala Gln Leu Gln Ala Val Pro Gly Ala Ala  
65                      70                      75                      80

Gln Tyr Ile Gly Leu Val Glu Ser Val Ala Gly Ser Cys Asn Asn Tyr  
85                      90                      95

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 154 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:



AATGTCACGT CCATTCATTC CCTCCTTGAC GAGGGGAAGC AGTCCCTGAC CAAGCTCGCA 120

GCGGCCTGGG GCGGTAGCGG TTCGGAAGCG TACC 154

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

Met Thr Glu Gln Gln Trp Asn Phe Ala Gly Ile Glu Ala Ala Ala Ser  
1 5 10 15

Ala Ile Gln Gly Asn Val Thr Ser Ile His Ser Leu Leu Asp Glu Gly  
20 25 30

Lys Gln Ser Leu Thr Lys Leu Ala Ala Ala Trp Gly Gly Ser Gly Ser  
35 40 45

Glu Ala Tyr  
50

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 282 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

CGGTCGCGCA CTTCCAGGTG ACTATGAAAG TCGGCTTCGG NCTGGAGGAT TCCTGAACCT	60
TCAAGCGCGG CCGATAACTG AGGTGCATCA TTAAGCGACT TTTCCAGAAC ATCCTGACGC	120
GCTCGAAACG CGGCACAGCC GACGGTGGCT CCGNCGAGGC GCTGNCTCCA AAATCCCTGA	180
GACAATTCGN CGGGGGCGCC TACAAGGAAG TCGGTGCTGA ATTCGNCNG TATCTGGTCG	240
ACCTGTGTGG TCTGNAGCCG GACGAAGCGG TGCTCGACGT CG	282

## (2) INFORMATION FOR SEQ ID NO:101:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1565 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

GTATGCGGCC ACTGAAGTCG CCAATGCGGC GGCGGCCAGC TAAGCCAGGA ACAGTCGGCA	60
CGAGAAACCA CGAGAAATAG GGACACGTAA TGGTGGATTT CGGGGCGTTA CCACCGGAGA	120
TCAACTCCGC GAGGATGTAC GCCGGCCCGG GTTCGGCCTC GCTGGTGGCC GCGGCTCAGA	180
TGTGGGACAG CGTGGCGAGT GACCTGTTTT CGGCCGCGTC GCGGTTTCAG TCGGTGGTCT	240
GGGGTCTGAC GGTGGGGTCG TGGATAGGTT CGTCGGCGGG TCTGATGGTG GCGGCGGCCT	300

TCGCCGAGAA CCGTGCTGAA CTGATGATTC TGATAGCGAC CAACCTCTTG GGGCAAAACA 480  
CCCCGGCGAT CCGGGTCAAC GAGGCCGAAT ACGGCGAGAT GTGGGCCCAA GACGCCGCCG 540  
CGATGTTTGG CTACGCCGCG GCGACGGCGA CGGCGACGGC GACGTTGCTG CCGTTCGAGG 600  
AGGCGCCGGA GATGACCAGC GCGGGTGGG TCCTCGAGCA GGCCGCCGCG GTCGAGGAGG 660  
CCTCCGACAC CGCCGGGGG AACCAGTTGA TGAACAATGT GCCCCAGGCG CTGCAACAGC 720  
TGGCCAGCC CACGCAGGGC ACCACGCCCTT CTCCAAGCT GGGTGGCCTG TGAAGACGG 780  
TCTCGCCGCA TCGGTGCGCG ATCAGCAACA TGGTGTCAAT GGCCAACAAC CACATGTCAA 840  
TGACCAACTC GGGTGTGTCA ATGACCAACA CCTTGAGCTC GATGTTGAAG GGCTTTGCTC 900  
CGGCGGCGGC CGCCAGGCC GTGCAAACCG CGGCGCAAAA CGGGGTCCGG GCGATGAGCT 960  
CGCTGGGCAG CTCGCTGGGT TCTTCGGGTC TGGGCGGTGG GGTGGCCGCC AACTTGGGTC 1020  
GGGCGGCCTC GGTGGTTTG TTGTCGGTGC CGCAGGCCTG GGCCGCGGCC AACCAGGCAG 1080  
TCACCCCGGC GCGCGGGCG CTGCCGCTGA CCAGCCTGAC CAGCGCCGCG GAAAGAGGGC 1140  
CCGGGCAGAT GCTGGGCGG CTGCCGGTGG GGCAGATGGG CGCCAGGGCC GGTGGTGGGC 1200  
TCAGTGGTGT GCTGCGTGT CCGCCGCGAC CCTATGTGAT GCCGCATTCT CCGGCGGCCG 1260  
GCTAGGAGAG GGGGCGCAGA CTGTCGTTAT TTGACCAGTG ATCGGCGGTC TCGGTGTTTC 1320  
CGCGGCCGCG TATGACAACA GTCAATGTGC ATGACAAGTT ACAGGTATTA GGTCCAGGTT 1380

GGCGTCCGCG CAAAACATTT CCGGTGCGGG CTGGAGTGGC ATGGCCGAGG CGACCTCGCT 1560

AGACA 1565

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 391 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

Met	Val	Asp	Phe	Gly	Ala	Leu	Pro	Pro	Glu	Ile	Asn	Ser	Ala	Arg	Met	
1				5					10					15		
Tyr	Ala	Gly	Pro	Gly	Ser	Ala	Ser	Leu	Val	Ala	Ala	Ala	Gln	Met	Trp	
			20					25					30			
Asp	Ser	Val	Ala	Ser	Asp	Leu	Phe	Ser	Ala	Ala	Ser	Ala	Phe	Gln	Ser	
		35				40					45					
Val	Val	Trp	Gly	Leu	Thr	Val	Gly	Ser	Trp	Ile	Gly	Ser	Ser	Ala	Gly	
	50					55				60						
Leu	Met	Val	Ala	Ala	Ala	Ser	Pro	Tyr	Val	Ala	Trp	Met	Ser	Val	Thr	
65					70					75				80		
Ala	Gly	Gln	Ala	Glu	Leu	Thr	Ala	Ala	Gln	Val	Arg	Val	Ala	Ala	Ala	
			85						90					95		

Glu Asn Arg Ala Glu Leu Met Ile Leu Ile Ala Thr Asn Leu Leu Gly  
115 120 125

Gln Asn Thr Pro Ala Ile Ala Val Asn Glu Ala Glu Tyr Gly Glu Met  
130 135 140

Trp Ala Gln Asp Ala Ala Ala Met Phe Gly Tyr Ala Ala Ala Thr Ala  
145 150 155 160

Thr Ala Thr Ala Thr Leu Leu Pro Phe Glu Glu Ala Pro Glu Met Thr  
165 170 175

Ser Ala Gly Gly Leu Leu Glu Gln Ala Ala Ala Val Glu Glu Ala Ser  
180 185 190

Asp Thr Ala Ala Ala Asn Gln Leu Met Asn Asn Val Pro Gln Ala Leu  
195 200 205

Gln Gln Leu Ala Gln Pro Thr Gln Gly Thr Thr Pro Ser Ser Lys Leu  
210 215 220

Gly Gly Leu Trp Lys Thr Val Ser Pro His Arg Ser Pro Ile Ser Asn  
225 230 235 240

Met Val Ser Met Ala Asn Asn His Met Ser Met Thr Asn Ser Gly Val  
245 250 255

Ser Met Thr Asn Thr Leu Ser Ser Met Leu Lys Gly Phe Ala Pro Ala  
260 265 270

Ala Ala Ala Gln Ala Val Gln Thr Ala Ala Gln Asn Gly Val Arg Ala  
275 280 285

Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser Leu Ser Val  
305 310 315 320

Pro Gln Ala Trp Ala Ala Ala Asn Gln Ala Val Thr Pro Ala Ala Arg  
325 330 335

Ala Leu Pro Leu Thr Ser Leu Thr Ser Ala Ala Glu Arg Gly Pro Gly  
340 345 350

Gln Met Leu Gly Gly Leu Pro Val Gly Gln Met Gly Ala Arg Ala Gly  
355 360 365

Gly Gly Leu Ser Gly Val Leu Arg Val Pro Pro Arg Pro Tyr Val Met  
370 375 380

Pro His Ser Pro Ala Ala Gly  
385 390

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 259 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:103:

ACCAACACCT TGCAC TCNAT GTTGAAGGGC TTAGCTCCGG CGGCGGCTCA GGCCGTGGAA 60  
ACCGCGGCGG AAAACGGGGT CTGGGCAATG AGCTCGCTGG GCAGCCAGCT GGGTTCGTGG 120

GGTTCGTTGT CGGTGCCGCC AGCATGGGCC GCGGCCAACC AGGCGGTCAC CCCGGCGGCG 240

CGGGCGCTGC CGCTGACCA 259

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 86 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

Thr Asn Thr Leu His Ser Met Leu Lys Gly Leu Ala Pro Ala Ala Ala  
1                      5                      10                      15

Gln Ala Val Glu Thr Ala Ala Glu Asn Gly Val Trp Ala Met Ser Ser  
20                      25                      30

Leu Gly Ser Gln Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu Gly Ala  
35                      40                      45

Gly Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser Leu Ser  
50                      55                      60

Val Pro Pro Ala Trp Ala Ala Ala Asn Gln Ala Val Thr Pro Ala Ala  
65                      70                      75                      80

Arg Ala Leu Pro Leu Thr  
85

(2) INFORMATION FOR SEQ ID NO:105:

(A) LENGTH: 1109 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

TACTTGAGAG AATTTGACCT GTTGCCGACG TTGTTTGCTG TCCATCATTG GTGCTAGTTA	60
TGGCCGAGCG GAAGGATTAT CGAAGTGGTG GACTTCGGGG CGTTACCACC GGAGATCAAC	120
TCCGCGAGGA TGTACGCCGG CCCGGGTTCG GCCTCGCTGG TGGCCGCCGC GAAGATGTGG	180
GACAGCGTGG CGAGTGACCT GTTTTCGGCC GCGTCGGCGT TTCAGTCGGT GGTCTGGGGT	240
CTGACGACGG GATCGTGGAT AGGTTCGTCG GCGGGTCTGA TGGTGGCGGC GGCCTCGCCG	300
TATGTGGCGT GGATGAGCGT CACCGCGGGG CAGGCCGAGC TGACCGCCGC CCAGGTCCGG	360
GTTGCTGCGG CGGCCTACGA GACGGCGTAT GGGCTGACGG TGCCCCCGCC GGTGATCGCC	420
GAGAACCGTG CTGAACTGAT GATTCTGATA GCGACCAACC TCTTGGGGCA AAACACCCCG	480
GCGATCGCGG TCAACGAGGC CGAATACGGG GAGATGTGGG CCCAAGACGC CGCCGCGATG	540
TTTGGCTACG CCGCCACGGC GGCGACGGCG ACCGAGGCGT TGCTGCCGTT CGAGGACGCC	600
CCACTGATCA CCAACCCCGG CGGGCTCCTT GAGCAGGCCG TCGCGGTGCA GGAGGCCATC	660
GACACGCGCG CGGCGAACCA GTTGATGAAC AATGTGCCCC AAGCGGTGCA ACAACTGGCC	720
CAGCCCACGA AAAGCATCTG GCCGTTGAC CAACTGAGTG AACTCTGGAA AGCCATCTCG	780



AACTCGGGTG TGTCATGGC CAGCACCTTG CACTCAATGT TGAAGGGCTT TGCTCCGGCG 900  
 GCGGCTCAGG CCGTGAAAC CGCGGCGCAA AACGGGGTCC AGGCGATGAG CTCGCTGGGC 960  
 AGCCAGCTGG GTTCGTCGCT GGGTTCTTCG GGTCTGGGCG CTGGGGTGGC GGCCAACCTG 1020  
 GGTCGGGCGG CCTCGGTCGG TTCGTTGTCG GTGCCGAGG CCTGGGCCGC GGCCAACCAG 1080  
 GCGGTCACCC CGGCGGCGCG GCGCTGCC 1109

## (2) INFORMATION FOR SEQ ID NO:106:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 341 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

Val Val Asp Phe Gly Ala Leu Pro Pro Glu Ile Asn Ser Ala Arg Met  
 1 5 10 15

Tyr Ala Gly Pro Gly Ser Ala Ser Leu Val Ala Ala Lys Met Trp  
 20 25 30

Asp Ser Val Ala Ser Asp Leu Phe Ser Ala Ala Ser Ala Phe Gln Ser  
 35 40 45

Val Val Trp Gly Leu Thr Thr Gly Ser Trp Ile Gly Ser Ser Ala Gly  
 50 55 60

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Ala Gly Gln Ala Glu Leu Thr Ala Ala Gln Val Arg Val Ala Ala Ala  
85 90 95

Ala Tyr Glu Thr Ala Tyr Gly Leu Thr Val Pro Pro Pro Val Ile Ala  
100 105 110

Glu Asn Arg Ala Glu Leu Met Ile Leu Ile Ala Thr Asn Leu Leu Gly  
115 120 125

Gln Asn Thr Pro Ala Ile Ala Val Asn Glu Ala Glu Tyr Gly Glu Met  
130 135 140

Trp Ala Gln Asp Ala Ala Ala Met Phe Gly Tyr Ala Ala Thr Ala Ala  
145 150 155 160

Thr Ala Thr Glu Ala Leu Leu Pro Phe Glu Asp Ala Pro Leu Ile Thr  
165 170 175

Asn Pro Gly Gly Leu Leu Glu Gln Ala Val Ala Val Glu Glu Ala Ile  
180 185 190

Asp Thr Ala Ala Ala Asn Gln Leu Met Asn Asn Val Pro Gln Ala Leu  
195 200 205

Gln Gln Leu Ala Gln Pro Thr Lys Ser Ile Trp Pro Phe Asp Gln Leu  
210 215 220

Ser Glu Leu Trp Lys Ala Ile Ser Pro His Leu Ser Pro Leu Ser Asn  
225 230 235 240

Ile Val Ser Met Leu Asn Asn His Val Ser Met Thr Asn Ser Gly Val  
245 250 255

Claims

1. A polypeptide comprising an antigenic portion of a soluble *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen has an N-terminal sequence selected from the group consisting of:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu (SEQ ID No. 115);
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser (SEQ ID No. 116);
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg (SEQ ID No. 17);
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro (SEQ ID No. 118);
- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val (SEQ ID No. 119);
- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro (SEQ ID No. 120);
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Thr-Ala-Ala-Ser-Pro-Pro-Ser (SEQ ID No. 121);
- (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly (SEQ ID No. 122);
- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn (SEQ ID No. 123); and
- (j) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 131)

wherein Xaa may be any amino acid.

2. A polypeptide comprising an immunogenic portion of an *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen has an N-terminal sequence selected from the group consisting of:

- (a) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 124) and
- (b) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 132), wherein Xaa may be any amino acid.

3. A polypeptide comprising an antigenic portion of a soluble *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos. 1, 2, 4-10, 13-25, 52, 94 and 96, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos. 1, 2, 4-10, 13-25, 52, 94 and 96 or a complement thereof under moderately stringent conditions.

4. A polypeptide comprising an antigenic portion of a *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos. 26-51, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos. 26-51 or a complement thereof under moderately stringent conditions.

5. A DNA molecule comprising a nucleotide sequence encoding a polypeptide according to any one of claims 1-4.

7. A host cell transformed with an expression vector according to claim 6.
8. The host cell of claim 7 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cells.
9. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:
  - (a) contacting a biological sample with one or more polypeptides according to any of claims 1-4; and
  - (b) detecting in the sample the presence of antibodies that bind to at least one of the polypeptides, thereby detecting *M. tuberculosis* infection in the biological sample.
10. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:
  - (a) contacting a biological sample with a polypeptide having an N-terminal sequence selected from the group consisting of sequences provided in SEQ ID No: 129 and 130; and
  - (b) detecting in the sample the presence of antibodies that bind to at least one of the polypeptides, thereby detecting *M. tuberculosis* infection in the biological sample.
11. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:
  - (a) contacting a biological sample with one or more polypeptides encoded by a DNA sequence selected from the group consisting of SEQ ID Nos. 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos. 3, 11 and 12; and
  - (b) detecting in the sample the presence of antibodies that bind to at least

12. The method of any one of claims 9-11 wherein step (a) additionally comprises contacting the biological sample with a 38 kD *M. tuberculosis* antigen and step (b) additionally comprises detecting in the sample the presence of antibodies that bind to the 38 kD *M. tuberculosis* antigen.
13. The method of any one of claims 9-11 wherein the polypeptide(s) are bound to a solid support.
14. The method of claim 13 wherein the solid support comprises nitrocellulose, latex or a plastic material.
15. The method of any one of claims 9-11 wherein the biological sample is selected from the group consisting of whole blood, serum, plasma, saliva, cerebrospinal fluid and urine.
16. The method of claim 15 wherein the biological sample is whole blood or serum.
17. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:
  - (a) contacting the sample with a first and a second oligonucleotide primer in a polymerase chain reaction, the first and the second oligonucleotide primers comprising at least about 10 contiguous nucleotides of a DNA molecule according to claim 5; and
  - (b) detecting in the sample a DNA sequence that amplifies in the presence of the first and second oligonucleotide primers, thereby detecting *M. tuberculosis* infection.
18. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

least about 10 contiguous nucleotides of a DNA sequence selected from the group consisting of SEQ ID Nos. 3, 11 and 12; and

(b) detecting in the sample a DNA sequence that amplifies in the presence of the first and second oligonucleotide primers, thereby detecting *M. tuberculosis* infection.

19. The method of claims 17 or 18 wherein the biological sample is selected from the group consisting of whole blood, sputum, serum, plasma, saliva, cerebrospinal fluid and urine.

20. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting the sample with one or more oligonucleotide probes comprising at least about 15 contiguous nucleotides of a DNA molecule according to claim 5; and

(b) detecting in the sample a DNA sequence that hybridizes to the oligonucleotide probe, thereby detecting *M. tuberculosis* infection.

21. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting the sample with one or more oligonucleotide probes comprising at least about 15 contiguous nucleotides of a DNA sequence selected from the group consisting of SEQ ID Nos. 3, 11 and 12; and

(b) detecting in the sample a DNA sequence that hybridizes to the oligonucleotide probe, thereby detecting *M. tuberculosis* infection.

22. The method of claims 20 or 21 wherein the biological sample is selected from the group consisting of whole blood, sputum, serum, plasma, saliva, cerebrospinal fluid and urine.

23. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting the biological sample with a binding agent which is capable of binding to a polypeptide according to any one of claims 1-4; and

(b) detecting in the sample a protein or polypeptide that binds to the binding agent, thereby detecting *M. tuberculosis* infection in the biological sample.

24. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting the biological sample with a binding agent which is capable of binding to a polypeptide having an N-terminal sequence selected from the group consisting of sequences provided in SEQ ID No: 129 and 130; and

(b) detecting in the sample a protein or polypeptide that binds to the binding agent, thereby detecting *M. tuberculosis* infection in the biological sample.

25. A method for detecting *M. tuberculosis* infection in a biological sample, comprising:

(a) contacting the biological sample with a binding agent which is capable of binding to a polypeptide encoded by a DNA sequence selected from the group consisting of SEQ ID Nos. 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos. 3, 11 and 12; and

(b) detecting in the sample a protein or polypeptide that binds to the binding agent, thereby detecting *M. tuberculosis* infection in the biological sample.

26. The method of any one of claims 23-25 wherein the binding agent is a monoclonal antibody.

27. The method of any one of claims 23-25 wherein the binding agent is



28. A diagnostic kit comprising:
  - (a) one or more polypeptides according to any of claims 1-4; and
  - (b) a detection reagent.
29. A diagnostic kit comprising:
  - (a) one or more polypeptides having an N-terminal sequence selected from the group consisting of sequences provided in SEQ ID No: 129 and 130; and
  - (b) a detection reagent.
30. A diagnostic kit comprising:
  - (a) one or more polypeptides encoded by a DNA sequence selected from the group consisting of SEQ ID Nos. 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos. 3, 11 and 12; and
  - (b) a detection reagent.
31. The kit of any one of claims 28-30 wherein the polypeptide(s) are immobilized on a solid support.
32. The kit of claim 31 wherein the solid support comprises nitrocellulose, latex or a plastic material.
33. The kit of any one of claims 28-30 wherein the detection reagent comprises a reporter group conjugated to a binding agent.
34. The kit of claim 33 wherein the binding agent is selected from the group consisting of anti-immunoglobulins, Protein G, Protein A and lectins.
35. The kit of claim 33 wherein the reporter group is selected from the

36. A diagnostic kit comprising a first polymerase chain reaction primer and a second polymerase chain reaction primer, the first and second primers each comprising at least about 10 contiguous nucleotides of a DNA molecule according to claim 5.

37. A diagnostic kit comprising a first polymerase chain reaction primer and a second polymerase chain reaction primer, the first and second primers each comprising at least about 10 contiguous nucleotides of a DNA sequence selected from the group consisting of SEQ ID Nos. 3, 11 and 12.

38. A diagnostic kit comprising at least one oligonucleotide probe, the oligonucleotide probe comprising at least about 15 contiguous nucleotides of a DNA molecule according to claim 5.

39. A diagnostic kit comprising at least one oligonucleotide probe, the oligonucleotide probe comprising at least about 15 contiguous nucleotides of a DNA sequence selected from the group consisting of SEQ ID Nos. 3, 11 and 12.

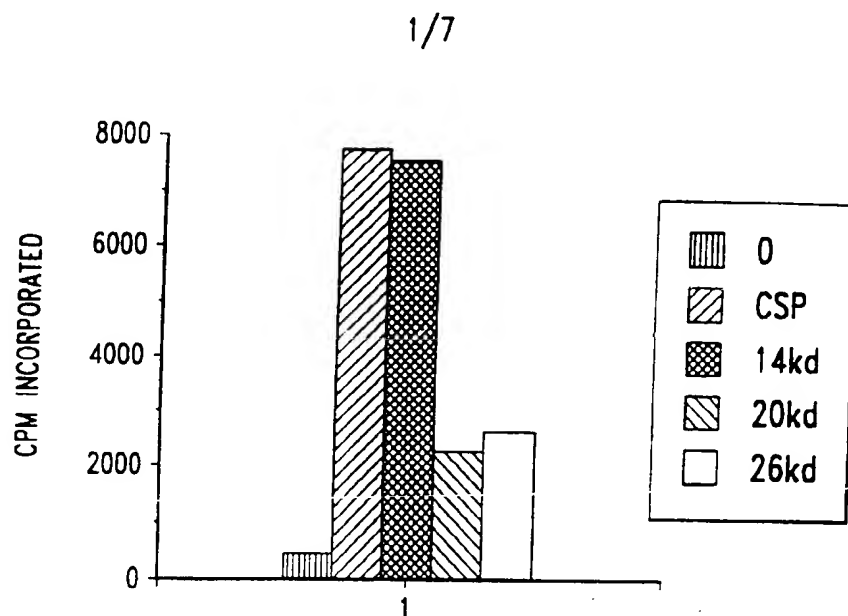
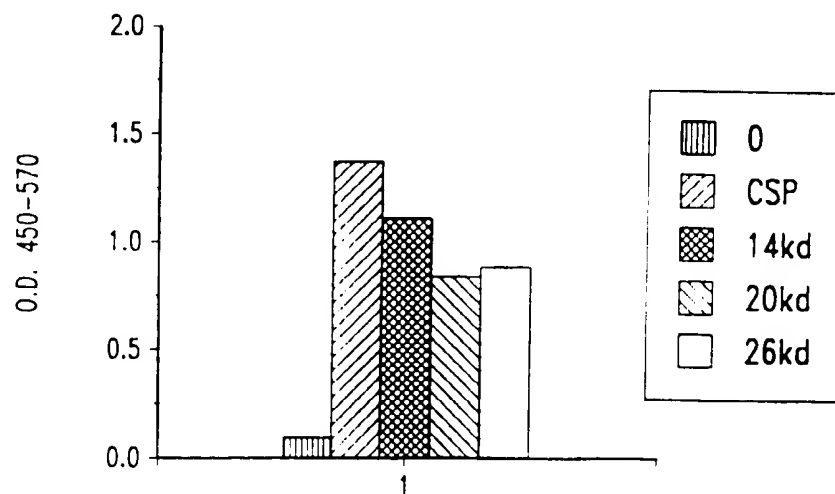
40. A monoclonal antibody that binds to a polypeptide according to any of claims 1-4.

41. A polyclonal antibody that binds to a polypeptide according to any of claims 1-4.

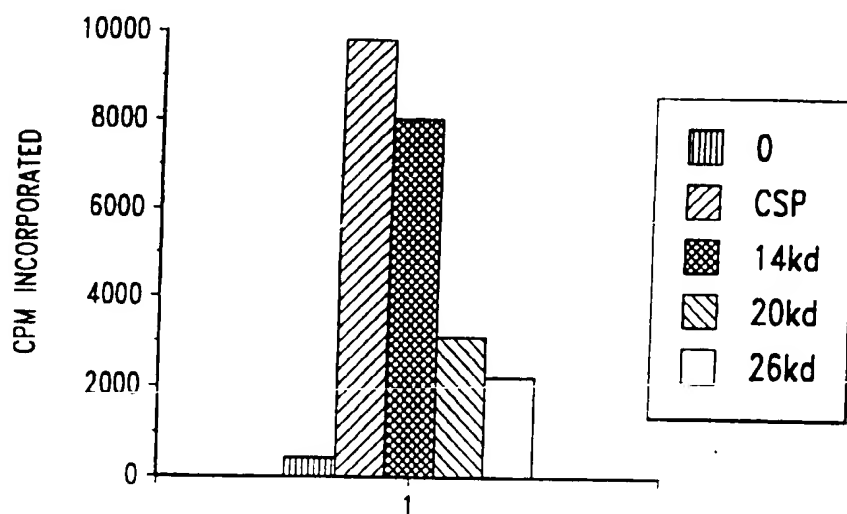
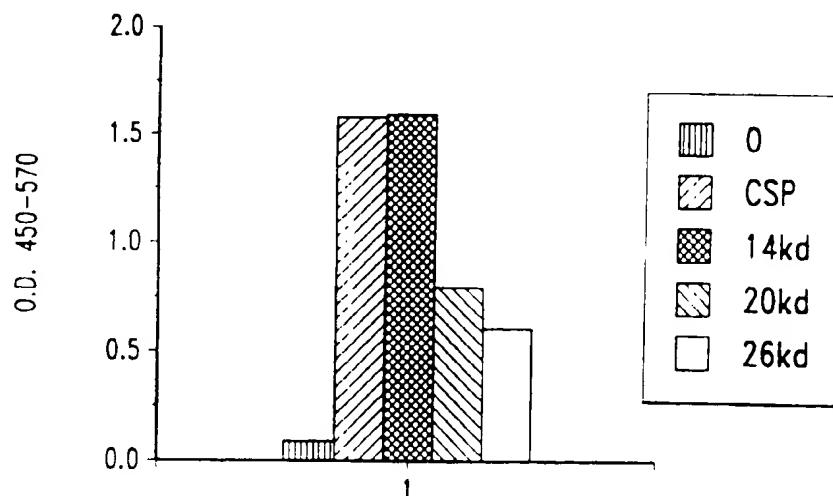
42. A fusion protein comprising two or more polypeptides according to any one of claims 1-4.

43. A fusion protein comprising one or more polypeptides according to

44. A fusion protein comprising a polypeptide having an N-terminal sequence selected from the group of sequences provided in SEQ ID Nos. 129 and 130.

*Fig. 1A**Fig. 1B*

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*Fig. 1C**Fig. 1D*

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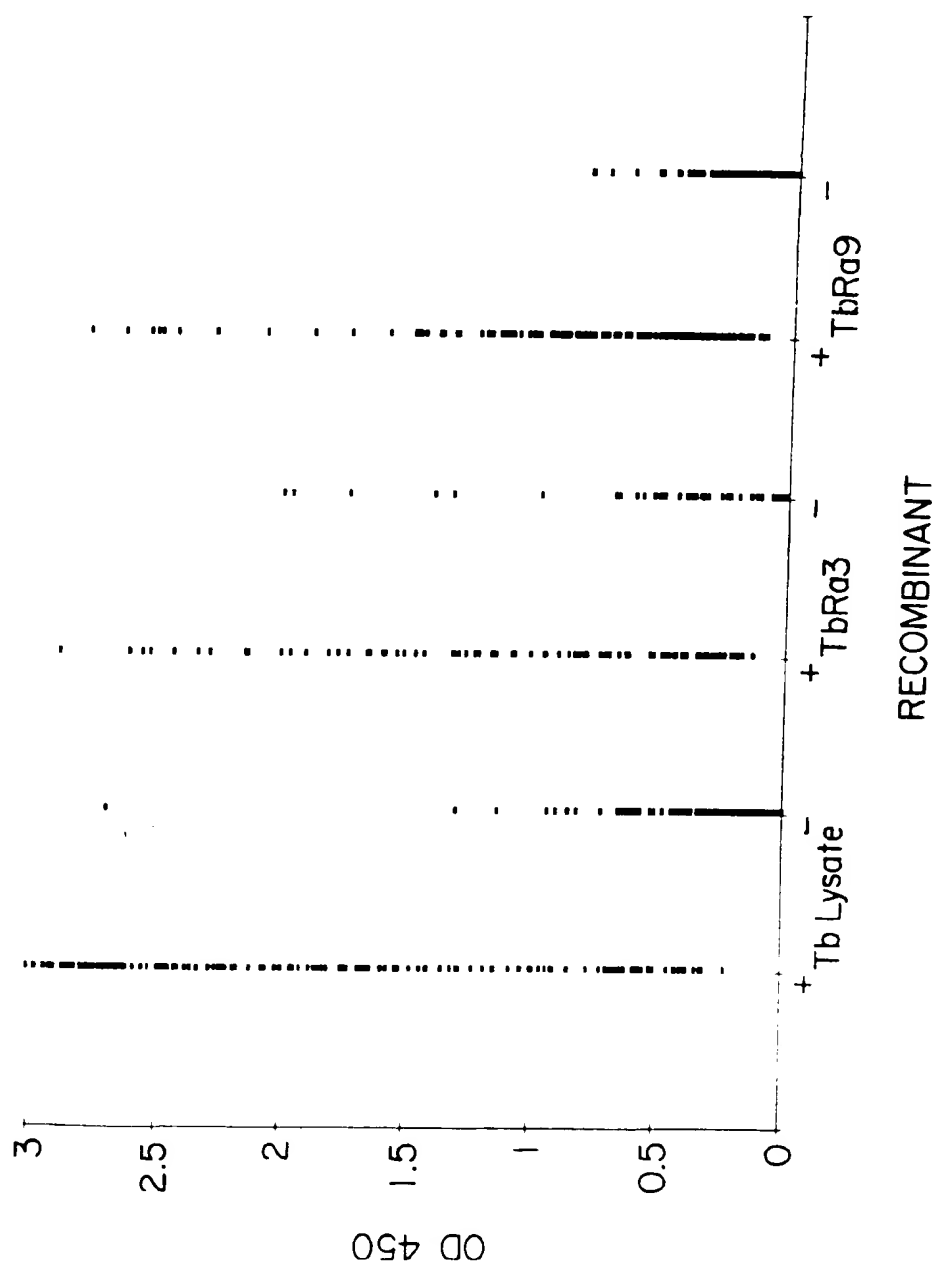


Fig. 2

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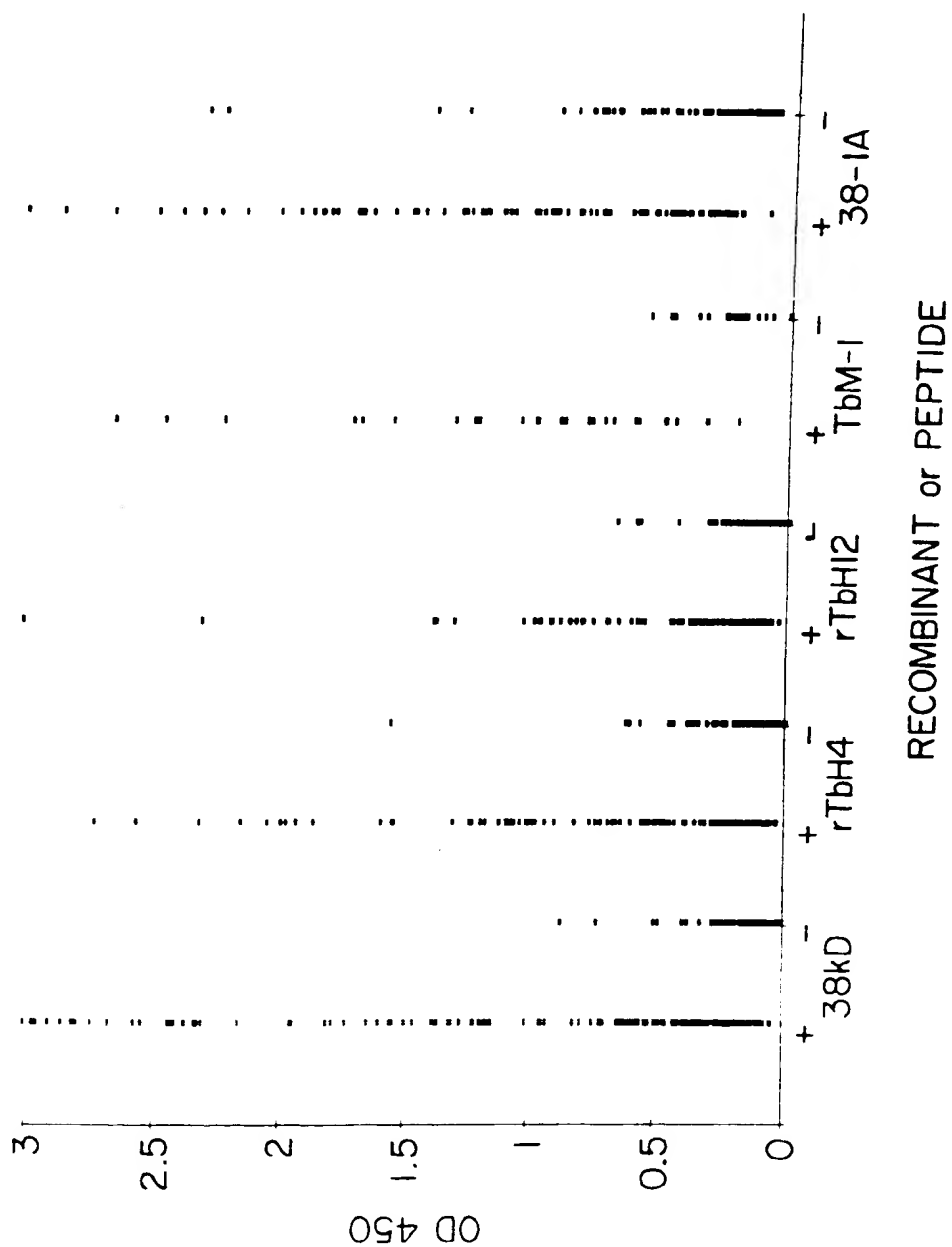


Fig. 3

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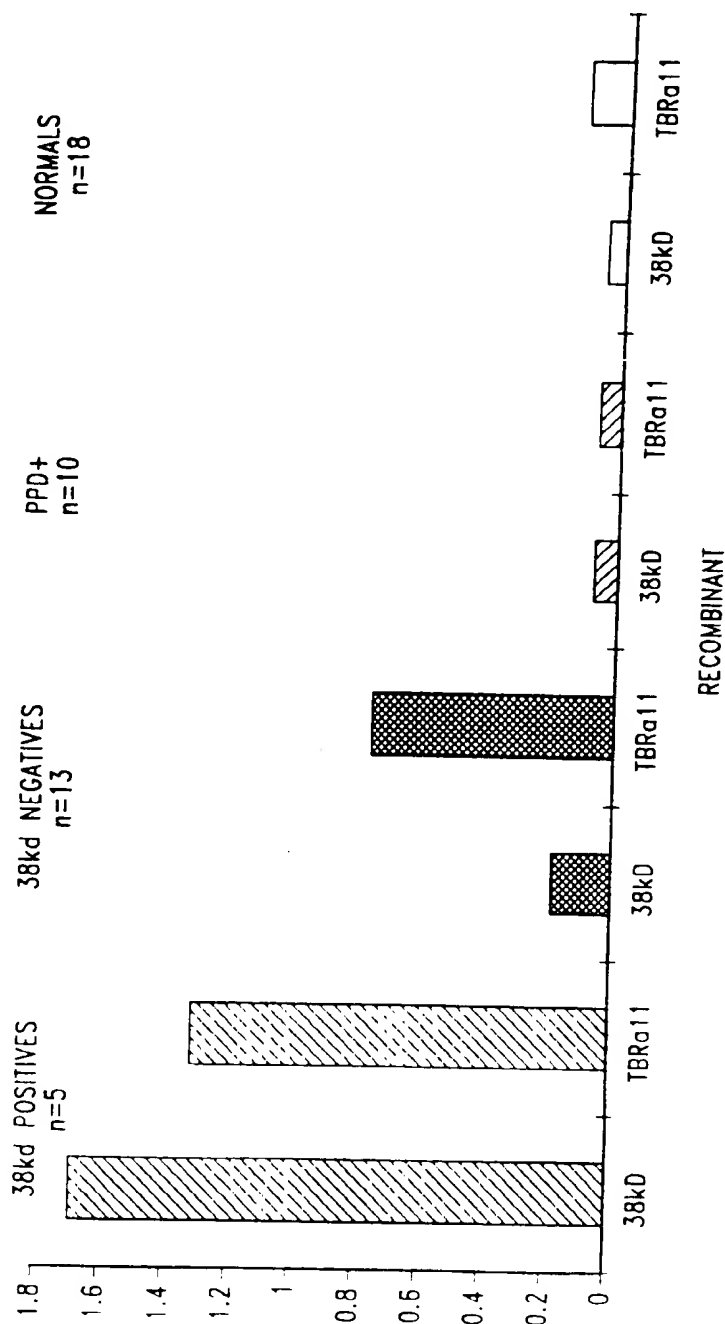


Fig. 4



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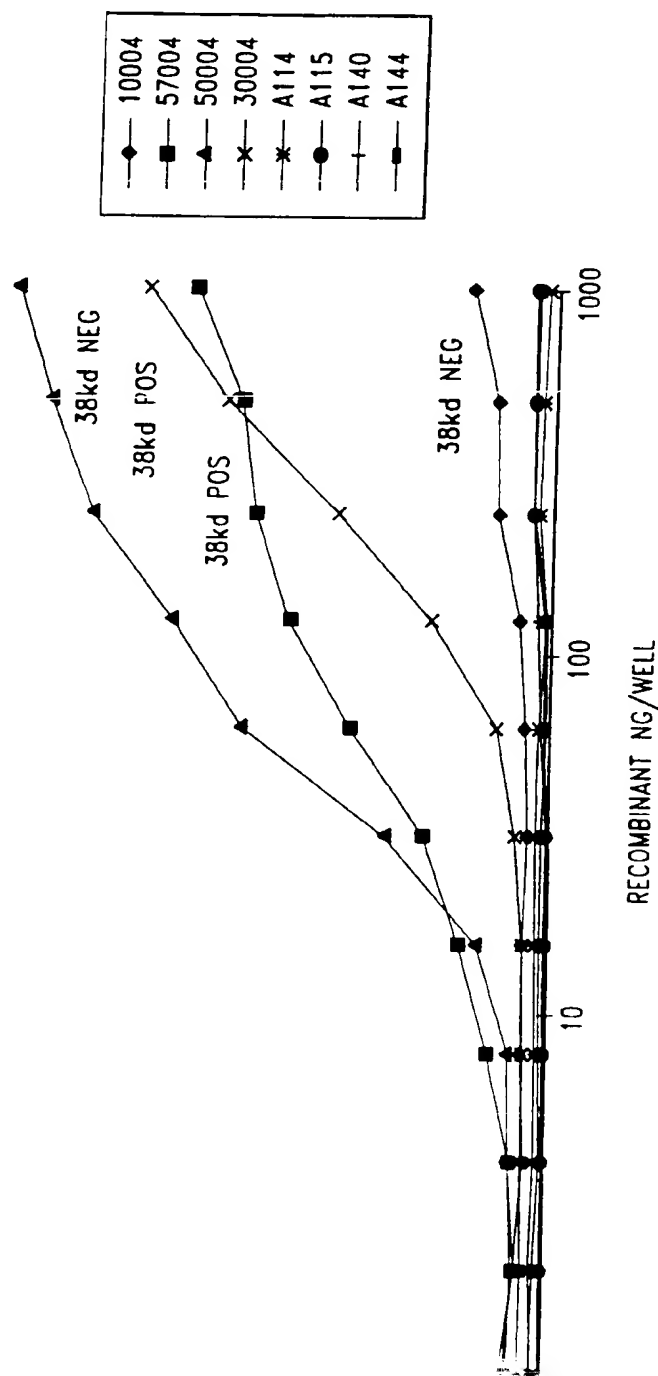


Fig. 5

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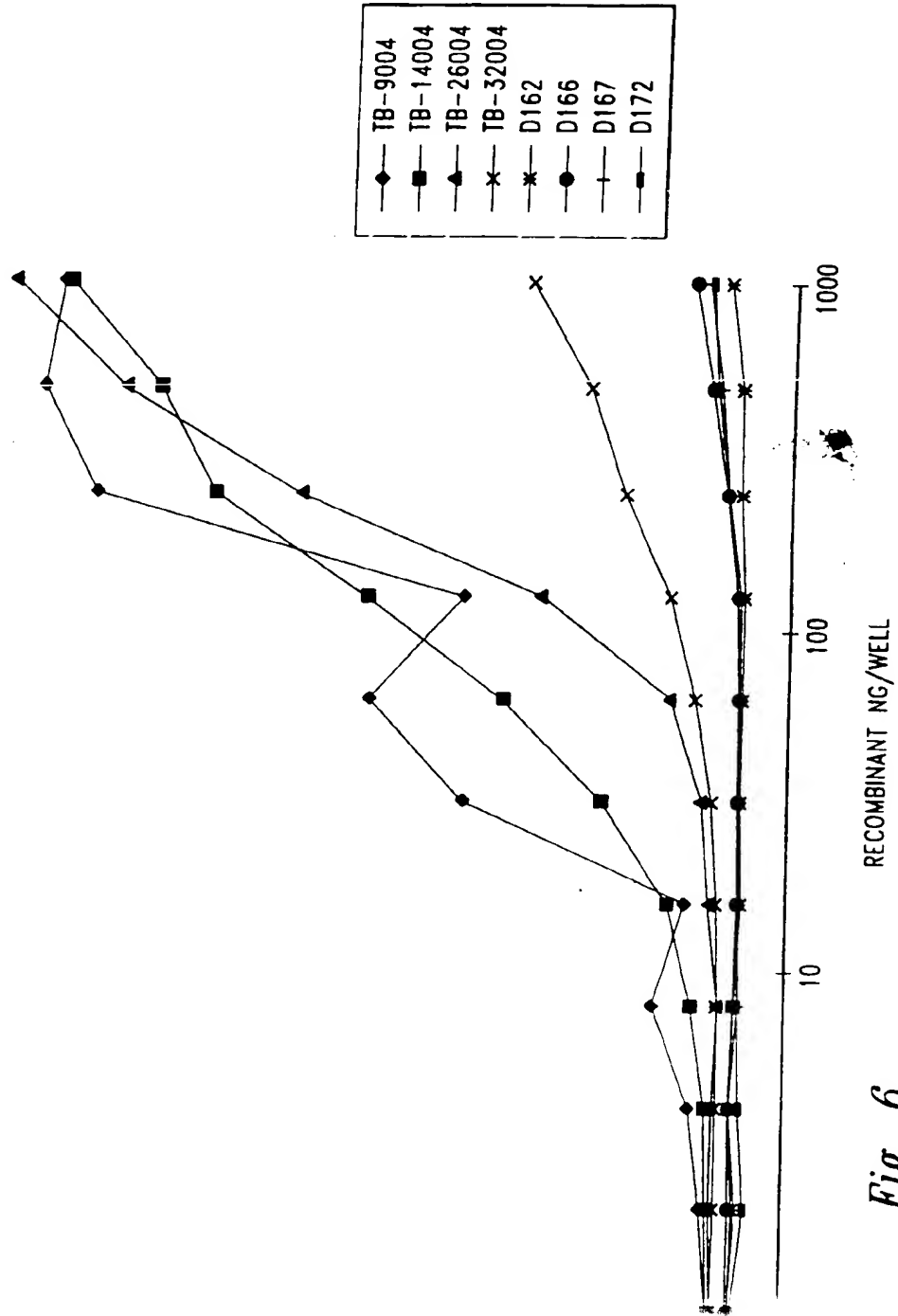


Fig. 6

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